DRAFT
TOXICOLOGICAL PROFILE FOR TETRACHLOROETHYLENE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for Tetrachloroethylene was released in 1996. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
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Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30333

Physical Mailing Address:
4770 Buford Highway
Building 106, 3rd floor, MS F-57
Chamblee, Georgia 30341

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Robin M. Ikeda, M.D., M.P.H.
Acting Assistant Administrator
Agency for Toxic Substances and Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials

incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Clinical Resources

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for tetrachloroethylene. The panel consisted of the following members:

1. Dr. Rodney R. Dietert, Professor of Immunotoxicology, College of Veterinary Medicine, Cornell University, Ithaca, New York;

2. Dr. Kelly G. Pennell, Civil and Environmental Engineering Department, University of Massachusetts-Dartmouth, North Dartmouth, Massachusetts; and

3. Jill E. Johnston, Department of Environmental Sciences & Engineering, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina.

These experts collectively have knowledge of tetrachloroethylene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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CONTENTS

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LIST OF FIGURES

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LIST OF TABLES

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1. PUBLIC HEALTH STATEMENT FOR TETRACHLOROETHYLENE

Overview

We define a public health statement and show how it can help you learn about tetrachloroethylene.

Introduction

A public health statement summarizes information about a hazardous substance. The information is taken from a toxicological profile developed by the Agency for Toxic Substances and Disease Registry's (ATSDR's) Division of Toxicology. A toxicological profile is a thorough review of a hazardous substance.

This toxicological profile examines tetrachloroethylene. This public health statement summarizes the Division of Toxicology and Human Health Science's findings on tetrachloroethylene, describes the effects of exposure to it, and describes what you can do to limit that exposure.

Tetrachloroethylene at hazardous waste sites

The U.S. Environmental Protection Agency (U.S. EPA) identifies the most serious hazardous waste sites in the nation. U.S. EPA then includes these sites the National Priorities List (NPL) and targets it for federal clean-up activities. U.S. EPA has found tetrachloroethylene in at least 945 of the 1,699 current or former NPL sites.

The total number of NPL sites evaluated for tetrachloroethylene is not known. But the possibility remains that as more sites are evaluated, the number of sites at which tetrachloroethylene is found may increase. This information is important; these future sites may be sources of exposure, and exposure to tetrachloroethylene may be harmful.

Tetrachloroethylene is present in many other non-NPL sites due to air, water, and soil contamination. The concern for tetrachloroethylene in non-NPL sites is greater than that of the NPL sites; the NPL sites represent a small fraction of the total hazardous waste sites that have been contaminated with tetrachloroethylene.

Why a tetrachloroethylene release can be harmful

When a contaminant is released from a large area such as an industrial plant or from a container such as a drum or bottle, it enters the environment. But such a release doesn't always lead to exposure. You can only be exposed to a contaminant when you come in contact with it. That contact—and therefore that exposure—can occur when you breathe, eat, or drink the contaminant, or when it touches your skin.

Even if you're exposed to tetrachloroethylene, you might not be harmed. Whether you are harmed will depend on such factors as the dose (how much), the duration (how long), and how you are exposed. Harm might also depend on whether you've been exposed to any other chemicals, as well as your age, sex, diet, family traits, lifestyle, and state of health.

A Closer Look at Tetrachloroethylene

Overview

This section describes tetrachloroethylene in detail and how you can be exposed to it.

What is tetrachloroethylene?

Tetrachloroethylene is a nonflammable colorless liquid. Other names for tetrachloroethylene include perchloroethylene, PCE, PERC, tetrachloroethene, and perchlor. Most people can smell tetrachloroethylene when it is present in the air at a level of 1 part in 1 million parts of air (ppm) or more. For more information, see Chapters 4 and 5.

How is tetrachloroethylene used?

Tetrachloroethylene is used as a dry cleaning agent and metal degreasing solvent. It is also used as a starting material (building block) for making other chemicals and is used in some consumer products.

How does tetrachloroethylene enter the environment?

Tetrachloroethylene can be released into the air, water, and soil at places where it is produced or used.

Exposure Sources or Pathways	Outcome
Air: Most releases of tetrachloroethylene during its use are directly to the atmosphere. Much of the tetrachloroethylene released into the air comes from the dry cleaning industry. Some Tetrachloroethylene may be released from dry-cleaned or consumer products.	Tetrachloroethylene breaks down very slowly in the air and so it can be transported long distances in the air. The average concentration of tetrachloroethylene in the air of the United States is typically less than 1 microgram per cubic meter of air.
Water: A variety of industries that use tetrachloroethylene (such as metal degreasing and dry cleaning) produce liquid wastes that contain the compound, which may then end up at waste treatment facilities.	Tetrachloroethylene evaporates quickly from water into air, although some tetrachloroethylene may remain in the water. It is generally slow to break down in water. Tetrachloroethylene can migrate through groundwater (or soil) up into the air of homes and buildings through vapor intrusion.
Soil: Contamination of soil can occur when tetrachloroethylene at a waste disposal site seeps out of the waste and into the soil.	Tetrachloroethylene may evaporate quickly from shallow soils or may filter through the soil and into the groundwater below. It is generally slow to break down in soil.

How Tetrachloroethylene Can Affect Your Health

Overview

This section looks at how tetrachloroethylene enters your body and potential tetrachloroethylene health effects found in human and animal studies.

How tetrachloro-ethylene enters your body

Tetrachloroethylene can enter your body from the air, water, or soil.

Possible Sources	Possible Exposure Pathway
Air	Tetrachloroethylene in air can easily enter your body when you breathe it in. Most of the tetrachloroethylene that you breathe in will go into your bloodstream and into other organs. A small amount of tetrachloroethylene in the air can also move through your skin and into your bloodstream.
Water	When tetrachloroethylene is found in water, it can enter your body when you drink or touch the water or when you breathe in steam from the water. Most of the tetrachloroethylene that you breathe in or drink will move from your stomach or lungs into your bloodstream. When you touch water containing tetrachloroethylene, some of it can get through your skin into your body, but not as much as when you breathe or swallow it.
Soil	You can be exposed to tetrachloroethylene in soil when small amounts of soil are transferred to your mouth accidentally, when your skin touches the soil, or when you breathe air or dust coming from the soil.

What happens to tetrachloro-ethylene in your body

A small amount of tetrachloroethylene in your blood may get changed into other chemicals. If you are exposed over and over again to tetrachloroethylene, some of it may be stored in body fat and the amount can build up over time. When the exposure stops, your body will slowly get rid of the tetrachloroethylene stored in fat.

How tetrachloro-ethylene leaves your body

If you have tetrachloroethylene in your blood, you will breathe most of it out very quickly. A small amount of tetrachloroethylene in your blood may get changed into other chemicals that leave your body in urine.

Tetrachloro-ethylene health effects

Tetrachloroethylene exposure may harm the nervous system, liver, kidneys, and reproductive system, and may be harmful to unborn children. If you are exposed to tetrachloroethylene, you may also be at a higher risk of getting certain types of cancer.

Short-term exposure effects

If you breathe in air containing a lot of tetrachloroethylene, you may become dizzy or sleepy, develop headaches, and become uncoordinated; exposure to very large amounts in the air can cause unconsciousness. Some people have died after being exposed in tanks or other small spaces, or after intentionally breathing in a large amount of tetrachloroethylene.

Long-term exposure effects

People who are exposed for longer periods of time to lower levels of tetrachloroethylene in air may have changes in mood, memory, attention, reaction time, or vision. Studies in animals exposed to tetrachloroethylene have shown liver and kidney effects, and changes in brain chemistry, but we do not know what these findings mean for humans.

Tetrachloroethylene may have effects on pregnancy and unborn children. Studies in people are not clear on this subject, but studies in animals show problems with pregnancy (such as miscarriage, birth defects, and slowed growth of the baby) after oral and inhalation exposure.

Tetrachloro-ethylene and cancer

Exposure to tetrachloroethylene for a long time may lead to a higher risk of getting cancer, but the type of cancer that may occur is not well-understood. Studies in humans suggest that exposure to tetrachloroethylene might lead to a higher risk of getting bladder cancer, multiple myeloma, or non-Hodgkin's lymphoma, but the evidence is not very strong. In animals, tetrachloroethylene has been shown to cause cancers of the liver, kidney, and blood system. It is not clear whether these effects might also occur in humans, because humans and animals differ in how their bodies handle tetrachloroethylene.

The EPA considers tetrachloroethylene to be "likely to be carcinogenic to humans by all routes of exposure" based on suggestive evidence in human studies and clear evidence of mononuclear cell leukemia in rats and liver tumors in mice exposed for 2 years by inhalation or stomach tube.

The International Agency for Research on Cancer considers tetrachloroethylene "probably carcinogenic to humans" based on limited evidence in humans and sufficient evidence in animals.

The National Toxicology Program considers tetrachloroethylene to be "reasonably anticipated to be a human carcinogen."

See Chapters 2 and 3 for more information on the health effects from exposure to tetrachloroethylene.

Children and Tetrachloroethylene

Overview

This section discusses potential health effects of tetrachloroethylene exposure in humans from when they're first conceived to 18 years of age, and how you might protect against such effects.

Exposure effects for children

It is not known whether children are more susceptible than adults to the effects of tetrachloroethylene. There are very few studies available to answer this question, and many more studies are needed.

What about birth defects?

We do not know for sure whether tetrachloroethylene can cause birth defects in humans. A few studies in humans have suggested that exposure to tetrachloroethylene increased the numbers of babies with heart, oral cleft, or neural tube defects, but these studies were not large enough to clearly answer the question. Studies in animals exposed by inhalation or stomach tube have not shown clear evidence of specific birth defects.

How Can Families Reduce the Risk of Exposure to Tetrachloroethylene

If your doctor finds that you have been exposed to significant amounts of tetrachloroethylene, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Food

Tetrachloroethylene has the potential to contaminate foods, although the levels found in food are generally low.

Drinking water

Contact local drinking water authorities and follow their advice if you have any concerns about the presence of tetrachloroethylene in your tap water.

Air

Tetrachloroethylene can be present in the indoor air of homes and apartments above dry cleaning facilities. To minimize risks associated with breathing in contaminated vapors, ensure that the area is well ventilated.

Contaminated groundwater or soil

Tetrachloroethylene can also be present in groundwater and soil underneath a building or a home, resulting in above-ground vapors through vapor intrusion (movement of vapors from groundwater or soil into air). If you think that you may have groundwater contaminated with tetrachloroethylene, contact your local state health department. In addition, a depressurization system, an increase in the air exchange rate between indoor and outdoor air, or vapor barriers can reduce exposure to tetrachloroethylene from vapor intrusion. Prevent children from playing in dirt or eating dirt if you live near a waste site that has tetrachloroethylene.

Check product labels for tetrachloro-ethylene

Tetrachloroethylene is widely used as a scouring solvent that removes oils from fabrics, as a carrier solvent, as a fabric finish or water repellant, and as a metal degreaser/cleaner. Follow instructions on product labels to minimize exposure to tetrachloroethylene. Storing these items in a shed or an outside location may reduce exposure and decrease the impact on indoor air.

Medical Tests to Determine Tetrachloroethylene Exposure

Overview

We identify medical tests that can detect whether tetrachloroethylene is in your body, and we recommend safe toxic-substance practices.

Tetrachloro-ethylene can be measured in blood and urine

Tetrachloroethylene and its breakdown products (metabolites) can be measured in blood and urine. However, the detection of tetrachloroethylene or its metabolites cannot predict the kind of health effects that might develop from that exposure. Because tetrachloroethylene and its metabolites leave the body fairly rapidly, the tests need to be conducted within days after exposure.

For more information on the different substances formed by tetrachloroethylene breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

Federal Government Recommendations to Protect Human Health

Overview

One way the federal government promotes public health is by regulating toxic substances or recommending ways to handle or to avoid toxic substances.

The federal government regulates toxic substances

Regulations are enforceable by law. The U.S. EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that have adopted toxic substances regulations.

The federal government recommends safe toxic substance practices

The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) have made recommendations about toxic substances. Unlike enforceable regulations, these recommendations are advisory only.

Toxic substance regulations

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

Some regulations and recommendations for tetrachloroethylene include:

Federal Organization	Regulation or Recommendation
U.S. Environmental Protection Agency (U.S. EPA)	EPA set a maximum contaminant level (MCL) of 0.005 milligrams per liter (mg/L; 5 ppb) as a national primary drinking standard for tetrachloroethylene and noted liver problems and increased risk of cancer as potential health effects from long-term exposure above the MCL.
Occupational Safety and Health Administration (OSHA)	OSHA has set an 8-hour time-weighted average permissible exposure limit of 100 ppm, an acceptable ceiling exposure limit of 200 ppm, and a maximum peak of 300 ppm (not to be exceeded for more than 5 minutes of any 3-hour period).
National Institute for Occupational Safety and Health (NIOSH)	NIOSH recommends that workplace exposure to tetrachloroethylene be minimized due to concerns about its carcinogenicity.

Additional Information

Overview

Where to find more information about tetrachloroethylene:

Who to contact

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

Additional information from ATSDR

ATSDR can provide publically available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

Where to obtain toxicological profile copies

Toxicological profiles are also available online at www.atsdr.cdc.gov. For more information:

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or
- Write to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
1600 Clifton Road NE
Mailstop F-57
Atlanta, GA 30333

For-profit organizations should request final toxicological profile copies from:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TETRACHLORO-ETHYLENE IN THE UNITED STATES

The use of tetrachloroethylene as a dry cleaning agent, chemical intermediate, and metal degreasing agent has led to its release to the environment. It has also been shown to be produced naturally by several temperate and subtropical marine macroalgae, but the majority of exposure to tetrachloroethylene is still through anthropogenic sources. It is primarily released to the air where it is slow to degrade, with estimated atmospheric half-lives of approximately 100 days. Data compiled from the EPA Air Quality System indicate that the ambient atmospheric level of tetrachloroethylene is typically <1 $\mu g/m^3$. Due to its long atmospheric half-life, it is subject to long-range transport and has been identified in atmospheric samples in remote locations such as Antarctica where no local sources of this substance exist. Levels for tetrachloroethylene in the indoor air tend to be higher. The median value for indoor air in the United States, from 2,195 entries in the EPA's database of volatile organic contaminants (VOC-AMBI), was approximately 4.9 $\mu g/m^3$, with an average value of 20.7 $\mu g/m^3$.

Tetrachloroethylene is a volatile liquid. When tetrachloroethylene is released to surface water or surface soil, it tends to volatilize quickly; however, tetrachloroethylene is also mobile in soil and has the potential to leach below the soil surface and contaminate groundwater and the air space between soil particles. Tetrachloroethylene can also biodegrade to trichloroethylene, dichloroethylene, vinyl chloride, and ethene through reductive dechlorination. Members of the population can also be exposed to the degradation product, trichloroethylene, which is often found as a contaminant in products with tetrachloroethylene. More information on trichloroethylene can be found in ATSDR's *Toxicological Profile for Trichloroethylene*.

Tetrachloroethylene was identified in approximately 4% of 3,498 aquifer samples at a median concentration of 0.090 µg/L in a U.S. Geological Survey (USGS) study. Tetrachloroethylene was among the 15 most frequently detected volatile organic compounds (VOCs). Sampling between 1985 and 1992 at a heavily contaminated site at Camp Lejeune, North Carolina, revealed tetrachloroethylene levels as high as 30,000 mg/L in water samples taken from hydrocone penetration sites, levels as much as 1,580 mg/L in water supply well samples, and levels >200 µg/L in tap water samples.

Tetrachloroethylene has been measured in some foods; however, these levels are generally low. Higher levels of tetrachloroethylene have been detected in foods that were in shops directly above dry cleaning facilities.

The most important routes of exposure to tetrachloroethylene for the general population appear to be inhalation of the compound in the outdoor (ambient) and indoor air and ingestion of drinking water. People working in the dry cleaning industries or using metal degreasing products may be exposed to elevated levels of tetrachloroethylene. In addition, people residing near contaminated sites or dry cleaning locations may also be exposed to higher levels than the general population. Exposure to tetrachloroethylene and other VOCs can also occur via soil vapor intrusion, which is of particular concern indoors). In addition, exposure can occur from background sources, or indoor sources other than vapor intrusion. Background indoor sources can include consumer products, building materials, combustion processes, dry-cleaned clothing or draperies, municipal tap water, or occupant activities. Tetrachloroethylene is one of the most commonly detected chemicals in background indoor sources.

Blood concentrations of tetrachloroethylene ranged from below the limit of detection up to 0.14 ng/mL in a random sampling of 1,317 participants in the 2003–2004 U.S. National Health and Nutrition Examination Survey (NHANES).

2.2 SUMMARY OF HEALTH EFFECTS

Available human and animal data indicate that the central nervous system is a primary target for tetrachloroethylene toxicity. Acute overexposure to tetrachloroethylene vapors results in effects that may include central nervous system depression, loss of consciousness, and even death, while neurobehavioral effects and vision changes are seen with prolonged exposure to concentrations as low as 2–10 ppm. Neurobehavioral changes occur at lower concentrations than other effects. Available animal data also identify the kidney, liver, reproductive system, and developing fetus as targets of tetrachloroethylene toxicity. Effects on the liver and kidney are believed to be mediated by metabolites of tetrachloroethylene, while the parent compound is considered to be the active neurotoxicant. Liver effects, including tumors, in mice may be induced primarily by oxidative metabolites, which are produced in larger quantities by mice than are produced in humans or rats. There is suggestive evidence for subtle perturbations of the immune system in animals exposed to tetrachloroethylene, but the data are limited and the relevance to humans is uncertain at present; further research is needed. Tetrachloroethylene has been shown to cause respiratory, ocular, and dermal irritation, as well as reduced body weight gain.

2. RELEVANCE TO PUBLIC HEALTH

Increased incidences of tumors in the kidney, liver, and lymphoid tissues have been reported in chronic bioassays of rats and mice exposed to tetrachloroethylene via inhalation and oral exposure routes. Available human data provide suggestive, but weak evidence for tetrachloroethylene-induced non-Hodgkin's lymphoma, multiple myeloma, and bladder cancer in humans.

The neurological symptoms of acute inhalation exposure to high levels of tetrachloroethylene are well documented in humans exposed accidentally and include headache, dizziness, drowsiness, ataxia, and mood changes; at higher levels, coma and seizures have occurred. Controlled human exposure studies using lower concentrations of tetrachloroethylene (50–100 ppm) for a few hours per day up to 5 days have also shown alterations in visual-evoked potentials and electroencephalograms (EEGs), as well as deficits in neurobehavioral tests for vigilance and eye-hand coordination.

Neurobehavioral effects have also been observed with prolonged occupational exposure to tetrachloroethylene. Deficits in behavioral tests that measured short-term memory for visual designs, reaction times, perceptual function, attention, and intellectual function were observed in dry cleaning workers exposed to concentrations between 8 and 15 ppm. In addition, loss of color vision (primarily in the blue-yellow range) has been reported in dry cleaning workers exposed to tetrachloroethylene at an average of 7.3 ppm for 2 years; this finding was supported by another study that did not quantify tetrachloroethylene exposure levels. A chronic inhalation Minimal Risk Level (MRL) of 0.006 ppm has been derived based on the lowest-observed-adverse-effect level (LOAEL) of 1.7 ppm identified in a study and supported by a follow-up study. This study was also used as the basis for the chronic oral MRL of 0.008 mg/kg/day, which was derived by route-to-route extrapolation using physiologically based pharmacokinetic (PBPK) modeling. In addition, the chronic-duration inhalation and chronic-duration oral MRLs were adopted as the acute- and intermediate-duration MRLs.

Several studies have been conducted examining neurological or visual function in small numbers of residents of buildings that also housed dry cleaning facilities. One of these studies observed increased reaction times and increased numbers of incorrectly-identified visual stimuli in exposed subjects compared with controls. Two other studies reported decreases in visual contrast sensitivity at low concentrations of tetrachloroethylene (0.05–0.3 ppm); however, these studies were potentially limited by selection bias and by deficiencies in the testing methods. Further studies of larger numbers of residentially-exposed persons are needed to confirm this finding.

Neurological effects of tetrachloroethylene exposure in laboratory rodents are qualitatively similar to those seen in human studies. Mice and rats have exhibited anesthetic effects after acute exposure to high concentrations (1,750 to 2,000 ppm), while acute- and intermediate-duration exposures to lower concentrations (200–1,000 ppm have resulted in effects on visual-evoked potentials, EEG patterns, and neurobehavioral tests in laboratory rodents. Alterations in brain chemistry were noted in rats and gerbils exposed to concentrations from 60 to 320 ppm. Neurological effects in animals exposed orally are similar to those seen after inhalation exposure, and have occurred at doses as low as 5 mg/kg/day.

The epidemiological database examining cancer end points in exposed humans is substantial, including more than 30 cohort or case-control studies, primarily in occupational settings. Upon critical review of the available epidemiological data regarding the possible carcinogenicity of tetrachloroethylene, the National Research Council (NRC) concluded that there was suggestive evidence for an association between tetrachloroethylene exposure and lymphoma, despite weak and sometimes inconsistent data. The NRC concluded that there was limited but insufficient evidence from epidemiological studies for an association with other cancer types including liver, kidney, esophageal, cervical, lung, and bladder cancer. After the NRC review, the EPA considered 27 additional epidemiological studies; these studies, with the data also reviewed by the NRC, formed the basis for the EPA conclusion that the epidemiological data supported a pattern of association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin’s lymphoma.

Animal studies have shown increases in liver cancer in mice exposed via inhalation and gavage, and mononuclear cell leukemia and kidney cancer in rats exposed via inhalation.

The U.S. EPA concluded that tetrachloroethylene is likely to be carcinogenic in humans by all routes of exposure based on sufficient evidence in animals and suggestive evidence of a causal association between tetrachloroethylene exposure in humans and bladder cancer, multiple myeloma, and non-Hodgkin’s lymphoma. The National Toxicology Program (NTP) concluded that tetrachloroethylene is reasonably anticipated to be a human carcinogen based on sufficient evidence in experimental animals. Based on increased risks of esophageal cancer, cervical cancer, and non-Hodgkin's lymphoma in several epidemiologic studies, and increased liver tumors in mice, increased mononuclear cell leukemia in rats, and renal tumors in male rats, the International Agency for Research on Cancer classified tetrachloroethylene as probably carcinogenic to humans (Group 2A).

2. RELEVANCE TO PUBLIC HEALTH

Tetrachloroethylene has been shown to cause hepatotoxic effects in humans following inhalation exposure and in animals exposed by the inhalation and oral routes. Mice are much more sensitive to the hepatic effects of tetrachloroethylene than rats or humans because of their higher rate of oxidative metabolism of tetrachloroethylene to trichloroacetic acid; trichloroacetic acid, and to a lesser extent dichloroacetic acid, is believed to be the primary hepatotoxic metabolite of tetrachloroethylene. Reversible kidney damage has been reported in humans accidentally exposed to acutely toxic amounts of tetrachloroethylene vapors. In addition, one study observed a significantly increased incidence of hypertensive end-stage renal disease among dry cleaning workers exposed to tetrachloroethylene. Studies of tetrachloroethylene exposure in animals have demonstrated renal effects in both rats and mice. Rats are more sensitive to the renal effects of tetrachloroethylene than mice; available data suggest that the rate of formation of reactive metabolites in the kidneys is higher in rats than mice or humans.

Few human data pertaining to immune system effects of tetrachloroethylene are available, and the studies conducted to date do not provide a clear picture of potential immunotoxic effects. Recent animal studies observed enhancement of antigen-stimulated allergic responses in rats and mice, and enhanced inflammation in rats, after exposure to very low oral doses of tetrachloroethylene (from 0.0009 to 0.09 mg/kg/day); however, the effects are of uncertain toxicological and human health relevance, as the degree of change that should be considered adverse is unclear. Additional study of the potential immunotoxicity of tetrachloroethylene is needed; this area represents a significant data gap.

The available epidemiological data on reproductive and developmental effects of exposure to tetrachloroethylene in occupational settings or in contaminated drinking water suffer from a number of limitations (including lack of measured exposure levels, coexposure to other solvents, lack of control for potential confounders, and small numbers of subjects) and do not provide sufficient bases to draw conclusions. Some studies have suggested that they may have an increased risk of adverse reproductive effects, primarily menstrual disorders and spontaneous abortions in women exposed occupationally. Other studies investigating the populations exposed via drinking water contamination have suggested that there may be an association between birth defects (especially oral cleft and neural tube defects) or growth retardation and tetrachloroethylene contamination.

In animals, increased pre- and post-implantation losses, decreased litter sizes, and decreased survival during lactation have been reported in rats and rabbits, but not in mice exposed during gestation to concentrations between 300 and 1,254 ppm. Decreased fetal and maternal weight and delayed skeletal development were observed in rats and mice exposed to concentrations of 300–664 ppm during gestation.

Gestational exposure to 900 ppm tetrachloroethylene was associated with behavioral and neurochemical alterations in some rat offspring. A gavage study in rats reported that tetrachloroethylene caused an increase in micro/anophthalmia in the offspring of rats treated by gavage with tetrachloroethylene at 900 mg/kg/day on gestation days 6–13. Following oral exposure of mice to 5 mg tetrachloroethylene/kg for 7 days beginning at 10 days of age, hyperactivity was observed at 60 days of age, but not at 17 days of age. Reduced *in vitro* fertilization was seen in the oocytes of rats exposed to 1,700 ppm for 2 weeks, and spermhead abnormalities were observed in mice exposed to 500 ppm for up to 10 weeks, suggesting possible effects on gametes.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for tetrachloroethylene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

- An MRL of 0.006 ppm has been derived for acute-duration inhalation exposure (14 days or less) to tetrachloroethylene.

Data available for acute-duration inhalation MRL derivation include three controlled human exposure studies and several animal studies. The lowest effect levels were identified in the human exposure studies

by Altmann et al. (1990, 1992). In the study by Altmann et al. (1992), male volunteers were exposed to tetrachloroethylene at 10 or 50 ppm, 4 hours/day for 4 days. Corresponding equivalent continuous exposure concentrations are 2 and 10 ppm. At 50 ppm, pattern reversal visual-evoked potential latencies increased ($p<0.05$) and significant performance deficits for vigilance ($p=0.04$) and eye-hand coordination ($p=0.05$) were observed. No effects on brainstem auditory-evoked potential were noted at either concentration. Because faint odor was reported by 33% of the subjects at 10 ppm and 29% of the subjects at 50 ppm on the first day of testing, and by 15% of the subjects at 10 ppm and 36% of the subjects at 50 ppm on the last day of testing, the investigators concluded that only a few subjects could identify their exposure condition. In a similar study by Altmann et al. (1990), significant ($p<0.05$) increased latencies for pattern reversal visual-evoked potentials were observed in 10 male volunteers exposed to tetrachloroethylene at 50 ppm, compared to 12 men exposed at 10 ppm. Exposures in this study were also 4 hours/day for 4 days, resulting in equivalent continuous exposure concentrations of 2 and 10 ppm. Effects on brainstem auditory-evoked potentials were not observed in the Altmann et al. (1990) study. Tetrachloroethylene in the blood increased with exposure duration, and linear regression to associate blood tetrachloroethylene with pattern reversal visual-evoked potential latencies was significant ($r=-0.45$, $p<0.03$). Additional tests of neurological function were not conducted in this study. These two studies identified a no-observed-adverse-effect level (NOAEL) of 2 ppm (equivalent continuous exposure concentration).

Hake and Stewart (1977) did not find any changes in flash-evoked potentials or equilibrium tests in four male subjects exposed to increasing concentrations of tetrachloroethylene 7.5 hours/day for 5 days. The subjects were sequentially exposed to 0, 20, 100, and 150 ppm (each concentration 1 week). Corresponding equivalent continuous exposure concentrations are 6.25, 31, and 47 ppm. Subjective evaluation of EEG scores suggested cortical depression in subjects exposed at 100 ppm. Decreases in the Flanagan coordination test were observed at ≥100 ppm.

Animal studies of acute-duration exposure to tetrachloroethylene have demonstrated neurological effects, but at higher concentrations than the human study by Altmann et al. (1990) (>16 ppm continuous equivalent concentration; Boyes et al. 2009; DeCeurriz et al. 1983; Mattsson et al. 1998; NTP 1986; Oshiro et al. 2008; Savolainen et al. 1977). PBPK modeling simulations suggest equivalent tetrachloroethylene blood areas under the curve (AUCs) for rats and humans exposed to the same inhaled concentrations (Chiu and Ginsberg 2011), indicating that the human-equivalent concentrations for these studies are also ≥16 ppm and higher than the human effect levels identified by Altmann et al. (1990,

1992). Thus, animal studies were not considered to be suitable options for acute-duration MRL derivation.

An acute-duration inhalation MRL could be obtained using the controlled human exposure study by Altmann et al. (1990, 1992). This study identified a NOAEL of 2 ppm (equivalent continuous exposure concentration) for neurobehavioral changes. This value is very close to the LOAEL of 1.7 ppm for color vision decrements in the chronic-duration epidemiological study by Cavalleri et al. (1994). Given that the NOAEL was from a study in which exposures were for only 4 hours/day for 4 days, it is uncertain whether this value would be adequately protective for longer exposures (up to 14 days). In male volunteers exposed to 1 ppm tetrachloroethylene for 6 hours, venous blood concentrations continued to increase between 4 and 6 hours (Chiu et al. 2007); likewise, when venous blood was sampled before each of four daily 4-hour exposures to tetrachloroethylene at 10 or 50 ppm, concentrations continued to increase each day from 36 µg/L before the second exposure to 10 ppm up to 56 µg/L 1 day after the fourth daily exposure (Altmann et al. 1990). These data suggest that continuous or repeated exposures over durations >4 days may yield higher blood levels than seen after four daily 4-hour exposures, and that the NOAEL of 2 ppm observed in the study by Altmann et al. (1990) may not be adequately protective for exposures up to 2 weeks. Because it is very close to the NOAEL from acute-duration exposure, the chronic-duration LOAEL of 1.7 ppm (continuous equivalent exposure concentration) from Cavalleri et al. (1994) represents a better basis for acute and intermediate-duration MRLs. A physiologically-based pharmacokinetic (PBPK) model (Chiu and Ginsberg 2011) was used to evaluate the effect of exposure duration on the arterial blood concentration of tetrachloroethylene and the area under the curve (AUC) of the blood concentration-time curve at a continuous exposure of 1.7 ppm. This simulation showed that arterial blood concentrations and 24-hour AUC blood concentration-time values are very similar after 14 days, 90 days, 365 days, and 2 years of exposure. These results predict that the blood AUC of tetrachloroethylene is nearly constant after 2 weeks of continuous exposure. The blood concentration reaches approximately 90% of steady-state at about 2 weeks of continuous exposure and 99% of steady state at 90 days. Given that the blood concentration of tetrachloroethylene after acute-duration exposure is very similar to that after chronic exposure to the same concentration, the chronic-duration inhalation MRL was adopted as the acute-duration inhalation MRL.

- An MRL of 0.006 ppm has been derived for intermediate-duration inhalation exposure (15–365 days) to tetrachloroethylene.

Epidemiological data in humans and studies in animals have identified the central nervous system as the system most affected at the lowest inhalation exposures. There are no intermediate-duration human

epidemiology studies. Available intermediate-duration studies that examined or observed neurological or neurobehavioral effects in animals (e.g., Karlsson et al. 1987; Kyrklund et al. 1988, 1990; Mattsson et al. 1992,1998; Rosengren et al. 1986; Tinston 1995; Wang et al. 1993) identified effect levels much higher than the acute-duration human studies (Altmann et al. 1990, 1992; Hake and Stewart,1977). In addition, the available data suggest that low effect levels in humans from acute-duration exposure are similar to those for the chronic-duration LOAEL of 1.7 ppm (continuous equivalent exposure concentration) from Cavalleri et al. (1994), suggesting that the same MRL is likely applicable to all exposure durations. A PBPK model (Chiu and Ginsberg 2011) was used to evaluate the effect of exposure duration on the arterial blood concentration of tetrachloroethylene and the AUC of the blood concentration-time curve at a continuous exposure of 1.7 ppm. This simulation showed that arterial blood concentrations and 24-hour AUC blood concentration-time values are very similar after 14 days, 90 days, 365 days, and 2 years of exposure. These results indicate that the blood concentration of tetrachloroethylene reaches steady-state at about 2 weeks of continuous exposure, and that longer exposure durations will not yield higher blood concentrations. Given that the blood concentration of tetrachloroethylene after acute-duration exposure is very similar to that after chronic exposure to the same concentration, the chronic-duration inhalation MRL was adopted as the intermediate-duration inhalation MRL.

- An MRL of 0.006 ppm has been derived for chronic-duration inhalation exposure (≥1 year) to tetrachloroethylene.

This MRL was derived from a study by Cavalleri et al. (1994) with support from a follow-up study by Gobba et al. (1998). Cavalleri et al. (1994) evaluated color vision in 35 tetrachloroethylene-exposed workers (22 dry-cleaners and 13 ironers). Color vision was evaluated by the Lanthany 15 Hue desaturated panel (D-15d) test, which is designed for early detection of acquired dyschromatopsia, and results were expressed as Color Confusion Index (CCI). Mean CCI scores were 1.192 ± 0.133 in dry cleaners compared with 1.089 ±0.117 in controls (p=0.007). Reexamination of the workers 2 years later showed that those workers whose exposure to tetrachloroethylene had increased experienced further decrements in color vision, while those whose exposure had decreased experienced no changes in color vision (Gobba et al. 1998). A LOAEL of 7.3 ppm was identified for this study.

The nervous system is a well-established target of tetrachloroethylene exposure in humans and animals, and effects on this system occur at lower concentrations than effects in other target organs such as the liver or kidney. A substantial number of studies evaluated the effects of inhaled tetrachloroethylene in occupationally exposed individuals, particularly those engaged in dry cleaning activities. More recent studies (Schreiber et al. 2002; Storm et al. 2011) have also provided suggestive evidence of changes in

visual contrast sensitivity at low concentrations (one-half to one-thirtieth of the continuous-equivalent concentration used to derive the MRL), in residential populations living in buildings that also housed dry cleaning facilities or in buildings in close proximity to such facilities. These studies were not selected for use due to limitations including small sample size and study design problems (lack of blinding of investigators, differences between exposed and referent groups that could confound the comparison) that weaken the conclusions that can be drawn from them. The human epidemiological studies in occupationally-exposed populations (especially Cavalleri et al. 1994; Echeverria et al. 1995;Gobba et al. 1998), combined with a small number of human controlled exposure experiments (Altmann et al. 1990; Hake and Stewart 1977), have identified central nervous system effects after acute and chronic-duration exposures to low-level exposures to tetrachloroethylene.

Neurological effects of tetrachloroethylene exposure in laboratory rodents are qualitatively similar to those seen in human studies. Mice and rats have exhibited anesthetic effects after acute exposure to high concentrations (Friberg et al. 1953; Goldberg et al. 1964; NTP 1986; Rowe et al. 1952), while lower concentrations have resulted in effects on visual-evoked potentials (Albee et al. 1991; Boyes et al. 2009; Mattsson et al. 1998), EEG patterns (Albee et al. 1991), neurobehavioral tests (Oshiro et al. 2008; Savolainen et al. 1977), and brain chemistry (Karlsson et al. 1987; Kyrklund et al. 1988; Rosengren et al. 1986; Wang et al. 1993) in laboratory rodents or gerbils.

The LOAEL of 7.3 ppm from Cavalleri et al. (1994) was converted to an equivalent continuous exposure concentration of 1.7 ppm (7.3 ppm x 8/24 hours x 5/7 days). Using the LOAEL of 1.7 ppm, a chronic-duration inhalation MRL of 0.006 ppm is obtained after application of an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL), and a modifying factor of 3 for database deficiencies (for inadequate information on potential low-dose immune system effects).

Oral MRLs

- An MRL of 0.008 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to tetrachloroethylene.

There is abundant evidence for neurological and neurobehavioral effects after chronic, low-level exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure are expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg

[2011]). Among human and animal studies identifying neurological or neurobehavioral effects after acute-duration oral exposure, the lowest effect level was identified by Fredriksson et al. (1993). Other acute-duration studies using rats and evaluating neurological responses used doses at least 10-fold higher. Fredriksson et al. (1993) identified a LOAEL of 5 mg/kg/day for hyperactivity in male NMRI mice exposed via gavage for 7 days beginning on postnatal day 10 (Fredriksson et al. 1993). Significant pharmacokinetic differences between mice and humans lead to markedly different blood levels of parent compound after oral exposure to tetrachloroethylene; thus, mice are not a good model for neurological effects of tetrachloroethylene exposure in humans. Furthermore, this LOAEL is similar to the LOAEL for chronic human exposure (2.3 mg/kg/day) obtained by route-to-route extrapolation from the inhalation study (Cavalleri et al. 1994) used to derive the chronic inhalation and oral MRLs. Inhalation studies (e.g., Altmann et al. 1990, 1992; Cavalleri et al. 1994) have shown that neurobehavioral effects occur at similar exposure levels after acute- and chronic-duration exposure. Given the lack of suitable acute-duration oral data, and based on the expectation that acute-duration effect levels in humans would be similar to chronic-duration effect levels, the acute-duration oral MRL was set equal to the chronic oral MRL.

- An MRL of 0.008 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to tetrachloroethylene.

There is abundant evidence for neurological and neurobehavioral effects at low exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure are expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg [2011]). Among human and animal studies of intermediate-duration oral exposure, only Chen et al. (2002) examined sensitive neurological or neurobehavioral effects. The 8-week study by Chen et al. (2002) identified a LOAEL of 3.6 mg/kg/day (adjusted to equivalent continuous dose from administered dose of 5 mg/kg/day, 5 days/week) for impaired nociception (increased latency to tail withdrawal from hot water and increased response latency to hot plate tests) and increased threshold for pentylenetetrazol-induced seizure initiation. PBPK modeling results reported by Chiu and Ginsberg (2011) indicate that the area under the tetrachloroethylene blood concentration-time curve for humans is about twice that of rats across a wide range of continuous oral doses (0.01–1,000 mg/kg/day). Thus, the human-equivalent LOAEL dose from the study by Chen et al. (2002) is 1.8 mg/kg/day. This LOAEL is very similar to the human oral LOAEL of 2.3 mg/kg/day obtained by route-to-route extrapolation from the Cavalleri et al. (1994) chronic inhalation study. Because the human data provide a better basis for MRL derivation than the rat data, the chronic-duration oral MRL was applied to all exposure durations.

- An MRL of 0.008 mg/kg/day has been derived for chronic-duration oral exposure (>1 year) to tetrachloroethylene.

The available human epidemiological studies of oral exposure to tetrachloroethylene do not provide sufficient exposure information to identify effect levels, and are thus not suitable for oral MRL derivation. The only available chronic-duration oral study of tetrachloroethylene in animals is the NCI (1977) cancer bioassay. In this study, survival was decreased at the lowest dose in both rats and mice; thus, it is also not suitable for use in deriving a chronic-duration oral MRL. There is abundant evidence for neurological and neurobehavioral effects after chronic, low exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure are expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg [2011]). Given the lack of suitable chronic-duration oral data, and the availability of a robust PBPK model for route-to-route extrapolation, the chronic-duration MRL was derived based on route-to-route extrapolation from the chronic-duration inhalation MRL. The internal dose metric chosen for route-to-route extrapolation was the 24-hour AUC of the tetrachloroethylene blood concentration-time curve. Based on simulations of the Chiu and Ginsberg (2011) model, a continuous inhalation exposure to 1.7 ppm yields the same 24-hour AUC as a continuous oral dose of 2.3 mg/kg/day. Using the LOAEL of 2.3 mg/kg/day, a chronic-duration oral MRL of 0.008 mg/kg/day is obtained after application of an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL), and a modifying factor of 3 for database deficiencies (for inadequate information on potential low-dose immune system effects).

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of tetrachloroethylene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. Significant study limitations are noted in this chapter if: (1) they help to explain disparate findings between studies; (2) only one or a few studies are available on a particular end point, meaning that the strength of the study is a relatively more important consideration; or (3) the limitations create substantial uncertainty in the conclusions.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between

"less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of tetrachloroethylene are indicated in Tables 3-1 and 3-3 and Figures 3-1 and 3-2.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

At high vapor concentrations, tetrachloroethylene is both a potent anesthetic agent and a cardiac epinephrine sensitizer. Sudden death resulting from acute exposure to high vapor concentrations is presumed to result from either excessive depression of the respiratory center or the onset of a fatal cardiac arrhythmia induced by epinephrine sensitization. Human deaths caused by tetrachloroethylene inhalation have been reported. While published reports have not included estimates or measurements of exposure concentrations in the air, postmortem blood concentrations of tetrachloroethylene in decedents have ranged from 44 to 66 mg/L (Dehon et al. 2000; Garnier et al. 1996; Isenschmid et al. 1998; Lukaszewski 1979).

A 33-year-old man was found unconscious after performing work on a plugged line in a commercial dry cleaning establishment and died on the way to the hospital (Lukaszewski 1979). Exposure to tetrachloroethylene was presumably by inhalation since an autopsy revealed no tetrachloroethylene in the stomach

contents, but high levels of the compound in the blood and brain (4.4 mg/100 mL and 36 mg/100 g, respectively). In another report, a 53-year-old male dry cleaner died after being overcome by tetrachloroethylene fumes (Levine et al. 1981). Tetrachloroethylene concentrations were 66 mg/L in blood, and 79, 31, and 46 mg/kg in the brain, heart, and lungs, respectively, of a 2-year-old boy found dead 1.5 hours after he was placed in his room with curtains that had been incorrectly dry cleaned in a coin-operated dry cleaning machine (Garnier et al. 1996). Isenschmid et al. (1998) reported that a 26-year old male was found dead after intentional inhalation of a pressurized tire repair product containing tetrachloroethylene and chlorodifluoromethane. Chlorodifluoromethane was not detected in biological specimens collected at autopsy; concentrations of tetrachloroethylene, in contrast, were 62 mg/L in blood, 341 mg/kg in the liver, and 47 mg/kg in the lung (Isenschmid et al. 1998). A 45-year-old woman was found unconscious in a laundry area and was transported to the hospital in a coma, where she was observed to exhibit acute respiratory distress syndrome and severe metabolic acidosis (Dehon et al. 2000). She died 7 days after the event from cardiovascular instability and acute renal failure. Autopsy findings included cerebral edema with foci of hemorrhagic infarction, diffuse lesions of edematous and hemorrhagic alveolitis with some foci of aspiration pneumonia in the lungs, diffuse hepatocytic necrosis, and acute renal tubular necrosis. Tetrachloroethylene was detected in the blood at 1.319 mg/L and in urine at 93 µg/g creatinine 2 days after hospital admission. Tissue levels ranged from 0.751 µg/g in muscle to 1.95 µg/g in the liver (Dehon et al. 2000). In these reports, the level of tetrachloroethylene exposure was not reported.

Retrospective cohort mortality studies of workers occupationally exposed to tetrachloroethylene for chronic durations have not suggested increased mortality associated with exposure. Although total mortality was not increased, Blair et al. (1979) found increased mortality from cancers of the lungs, cervix, uterus, and skin among dry cleaners. This study is limited by a lack of control for alcohol and tobacco consumption. Other studies have not shown significantly increased mortality in workers (dry cleaners or aircraft maintenance workers) occupationally exposed to tetrachloroethylene (Blair et al. 1990; Brown and Kaplan 1987; Katz and Jowett 1981; Spirtas et al. 1991). These studies did not include exposure measurements, but relied on job descriptions, work history as a surrogate for exposure duration, and/or estimated exposure concentrations.

There were no major differences between mice and rats in susceptibility to lethal effects of tetrachloroethylene following acute-duration exposure. In addition, no sex differences in response were detected. A 4-hour inhalation LC_{50} of 5,200 ppm for female albino mice has been reported (Friberg et al. 1953); LC_{50} data in other species are not available. The highest nonlethal concentrations reported for

4-hour exposure to tetrachloroethylene were 2,000 to 2,450 ppm in mice (Friberg et al. 1953; NTP 1986; Rowe et al. 1952) and 2,445 ppm in rats (NTP 1986). The lowest lethal concentrations reported for 4-hour exposures were 2,613–3,000 ppm in mice (Friberg et al. 1953; NTP 1986) and 3,786 ppm in rats (NTP 1986). A single 10- or 14-hour exposure of rats to 2,000 ppm did not produce death, while death occurred with exposure to 3,000 ppm for ≥5 hours (Rowe et al. 1952). In a 14-day study of rats and mice, mortality occurred in rats exposed to 1,750 ppm tetrachloroethylene but not in mice (NTP 1986). Compound-related mortality did not occur in either species at exposure concentrations of ≤875 ppm. A 2-week study in F344 rats and Crj:BDF1 mice reported mortality at 3,200 ppm in both species, but not at 1,600 ppm when administered 6 hours/day, 5 days/week (JISA 1993).

In an intermediate-duration study, increased mortality occurred in rats and mice exposed to 1,600 ppm tetrachloroethylene for 13 weeks, but not in those exposed to concentrations ≤800 ppm (NTP 1986). No deaths were reported in a different 13-week study of rats and mice exposed to concentrations up to 1,400 ppm tetrachloroethylene (JISA 1993). Mortality in rats exposed to 400 ppm tetrachloroethylene and mice exposed to 100 or 200 ppm tetrachloroethylene by inhalation in a 103-week carcinogenesis bioassay was a result of compound-related lesions and neoplasms (NTP 1986). This study is discussed in Sections 3.2.1.2 and 3.2.1.7. Survival was reduced in another chronic bioassay of rats and mice exposed to 600 and 250 ppm tetrachloroethylene for 104 weeks (JISA 1993). The study authors did not indicate whether the decreased survival was attributable to neoplasia.

All reliable LOAEL and LC_{50} values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

No studies were located regarding dermal effects in humans or animals after inhalation exposure to tetrachloroethylene.

Respiratory Effects. Data on the respiratory effects of tetrachloroethylene exposure in humans are limited to case reports (Carpenter 1937; Patel et al. 1973; Rowe et al. 1952; Tanios et al. 2004) and two experimental studies (Rowe et al. 1952; Stewart et al. 1981). The studies reporting exposure

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d				3200 (5 M and 7 F died)	JISA 1993	
2	Rat (Fischer- 344)	2wk 5d/wk 6hr/d				1750 (5/10 rats died)	NTP 1986	
3	Rat (Fischer- 344)	4 hr				3786 (5/10 rats died)	NTP 1986	
4	Rat (albino)	4 hours		2000 F		4000 F (increased mortality)	Union Carbide 1962	
5	Mouse (NS)	4 hr				5200 F (LC50)	Friberg et al. 1953	
6	Mouse (Hybrid)	2 wk 5 d/wk 6 hr/d				3200 (9 M and 7 F died)	JISA 1993	
7	Mouse (B6C3F1)	4 hr				2613 F (2/5 died)	NTP 1986	
Systemic								
8	Human	3 hr	Cardio	87 M			Ogata et al. 1971	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
9	Human	0.05-2 hr	Resp	106	216	(irritation)	930	(severe irritation tolerated for <2 minutes)	Rowe et al. 1952	
			Ocular		106	(slight ocular irritation)	930	(severe irritation tolerated for <2 minutes)		
10	Human	5d 7.5hr/d	Resp	150 M					Stewart et al. 1981	
			Cardio	150 M						
			Hemato	150 M						
			Hepatic	150 M						
			Renal	150 M						
11	Rat (CD)	Gd 6-19 7 d/wk 6 hr/d	Bd Wt	65 F	249 F	(19% decr in maternal body weight gain during Gd 6-9)			Carney et al. 2006	
12	Rat (Fischer- 344)	2wk 5d/wk 6hr/d	Bd Wt	875 M			1750 M	(body weight 28% lower than controls)	NTP 1986	
13	Rat (Fischer- 344)	14d 6hr/d	Hepatic		400	(hypertrophy)			Odum et al. 1988	
			Renal	400						

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
14	Rat (Sprague-Dawley)	4 hrs/day, 8 days	Hepatic	1000 M			Piper and Sparschu 1969	
			Renal		1000 M increased kidney weight, pale kidneys, minimal to moderate hyaline droplet formation			
			Bd Wt	1000 M				
15	Rat (Sprague-Dawley)	7 hrs/day, 8 days	Hepatic	1000 M			Piper and Sparschu 1969	
			Renal		1000 M increased absolute kidney weight, pale kidneys, minimal to moderate hyaline droplet formation			
			Bd Wt	1000 M				
16	Rat (Long- Evans)	6 hrs/day, 5 d/wk; 2 wks pre-mating-matin	Hepatic	1000 F			Tepe et al. 1980	
			Bd Wt	1000 F				

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
17	Mouse (ddY)	5d 6hr/d	Resp		300 M (epithelial degeneration of olfactory mucosa, dilation of Bowman's glands, atrophy of olfactory nerves)		Aoki et al. 1994	
18	Mouse (Hybrid)	2 wk 5 d/wk 6 hr/d	Hepatic	800	1600 (central enlargement of liver)		JISA 1993	
			Renal	400	800 (necrosis and regeneration of proximal tubules)			
19	Mouse (NS)	4 hr	Hepatic		200 F (fatty degeneration)		Kylin et al. 1963	
20	Mouse (B6C3F1)	2wk 5d/wk 6hr/d	Hepatic	425	875 (hepatic vacuolization)		NTP 1986	
			Bd Wt	1750				
21	Mouse (B6C3F1)	14d 6hr/d	Hepatic		400 (peroxisomal proliferation; fatty changes)		Odum et al. 1988	
			Renal	400				

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
22	Mouse (ddy)	5 days; 6 hrs/day	Resp		300 M (erosion of the nasal mucosa)		Suzaki et al. 1997	
23	Mouse C57BL	Gd 7-15 8 hr/d	Hepatic		664 F (Increased relative liver weight)		Szakmary et al. 1997	
			Bd Wt	664 F				
24	Dog (Beagle)	10 min	Resp	5000 M	10000 M (upper respiratory tract irritation)		Reinhardt et al. 1973	
			Cardio	10000 M				
25	Rabbit (New Zealand)	Gd 7-20 8 hr/d	Bd Wt			1254 F (58% lower body weight gain)	Szakmary et al. 1997	
Neurological								
26	Human	4d 4hr/d		10 M	50 M (increased latency of pattern reversal visual-evoked potentials)		Altmann et al. 1990	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
27	Human	4d 4hr/d		10 M	50 M	(increased latency of pattern reversal visual-evoked potential, significant performance deficits for vigilance and eye-hand coordination)			Altmann et al. 1992	
28	Human	<3 hr		500	1000	(mood/personality changes)	2000	(anesthesia)	Carpenter 1937	
29	Human	5 d 7.5hr/d		20	100	(cerebral cortical depression)			Hake and Stewart 1977; Stewart et al. 1981	
30	Human	3 hr		87 M					Ogata et al. 1971	
31	Human	0.05-2 hr		106	216	(dizziness/sleepiness)	280	(incoordination)	Rowe et al. 1952	
32	Human	5d 7hr/d			101	(mood/personality changes)			Stewart et al. 1970	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
33	Rat (Long- Evans)	Once 1.5 hr			250 M (reduced amplitude of visual evoked potentials)		Boyes et al. 2009	
34	Rat (Fischer- 344)	4 d 6 hr/d			800 M (altered flash and somatosensory evoked potentials and EEG)		Mattsson et al. 1998	
35	Rat (Fischer- 344)	2wk 5d/wk 6hr/d		875		1750 (hypoactivity; ataxia)	NTP 1986	
36	Rat (Long- Evans)	once 1 hr/d			500 M (impaired sustained attention)		Oshiro et al. 2008	
37	Rat (Sprague-Dawley)	4d 6hr/d			200 M (increased open-field behavior, i.e., ambulation)		Savolainen et al. 1977	
38	Rat (albino)	4 hours			2000 F (loss of consciousness and anesthesia)		Union Carbide 1962	
39	Mouse (Swiss-Webster)	1 d 4 hr/d			596 M (prolongation of escape-directed behavior)		DeCeaurriz et al. 1983	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
40	Mouse (B6C3F1)	2wk 5d/wk 6hr/d		875		1750 (anesthesia)	NTP 1986	
41	Mouse (B6C3F1)	4 hr				2328 (anesthesia)	NTP 1986	
Reproductive								
42	Rat (Sprague-Dawley)	2 wk 2 periods/day 1 hr/period (W)			1700 F (reduced in vitro fertilizability of oocytes from treated rats)		Berger and Horner 2003	
43	Rat (CD)	GD 6-19 7 d/wk 6 hr/d		600 F			Carney et al. 2006	
44	Rat (albino)	up to 10 weeks		500 M			NIOSH 1980	
45	Rat (albino)	GD 6-18 (7 hrs/day)		500 F			NIOSH 1980	
46	Rat (Long- Evans)	6 hrs/day, 5 d/wk, 2 wks pre-mating-mati		1000 F			Tepe et al. 1980	
47	Mouse (CD-1)	up to 10 weeks		100 M	500 M (significant increase in spermhead abnormalities)		NIOSH 1980	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
48	Mouse C57BL	Gd 7-15 8 hr/d		664 F			Szakmary et al. 1997	
49	Rabbit (New Zealand)	GD 7-21 (7 hrs/day)		500 F			NIOSH 1980	
50	Rabbit (New Zealand)	Gd 7-20 8 hr/d				1254 F (4/16 litters totally resorbed; increased postimplantation loss)	Szakmary et al. 1997	
Developmental								
51	Rat (CD)	GD 6-19 7 d/wk 6 hr/d		250	600 (decr fetal weight and incomplete ossification of thoracic vertebral centra)		Carney et al. 2006	
52	Rat (Sprague-Dawley)	Gd 14-20 7hr/d		100 F	900 F (transient decreased performance ascent test; decreased brain acetylcholinesterase; increased open-field activity)		Nelson et al. 1980	
53	Rat (albino)	GD 6-18 (7 hrs/day)		500			NIOSH 1980	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
54	Rat (Sprague-Dawley)	Gd6-15 7hr/d				300 F (increased fetal resorptions)	Schwetz et al. 1975	
55	Mouse (Swiss-Webster)	Gd6-15 7hr/d			300 F (decreased fetal weight; delayed ossification)		Schwetz et al. 1975	
56	Mouse C57BL	Gd 7-15 8 hr/d				664 (increased percentage of fetuses with internal malformations)	Szakmary et al. 1997	
57	Rabbit (New Zealand)	GD 7-21 (7 hrs/day)		500			NIOSH 1980	
58	Rabbit (New Zealand)	Gd 7-20 8 hr/d				1254 (4/16 litters totally resorbed; increased postimplantation loss)	Szakmary et al. 1997	
INTERMEDIATE EXPOSURE								
Death								
59	Rat (Fischer- 344)	13wk 5d/wk 6hr/d				1600 (11/20 rats died)	NTP 1986	
60	Mouse (B6C3F1)	13wk 5d/wk 6hr/d				1600 (6/10 mice died)	NTP 1986	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Systemic								
61	Rat (Sprague-Dawley)	6 hrs/day, 5 days/wk. 4 weeks	Hepatic	100 F	300 F (increased relative liver weight)		Boverhof et al. 2012	
			Bd Wt	300 F	1000 F (transient decrease in body weight)			
62	Rat (NS)	7mo 5d/wk 8hr/d	Hepatic	70	230 (decreased glycogen)		Carpenter 1937	
			Renal	230	470 (mild nephropathy)			
63	Rat (Fischer- 344)	28d 6hr/d	Renal	400			Green et al. 1990	
64	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Bd Wt	609 M	1400 M (decreased body weight gain)		JISA 1993	
65	Rat (Sprague-Dawley)	90 d	Hepatic		320 M (increased liver weights)		Kyrklund et al. 1990	
66	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d	Resp	800	1600 (lung congestion)		NTP 1986	
			Hepatic	200	400 liver congestion			
			Bd Wt	800 M		1600 M (body weight 20% lower than controls)		

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
67	Rat (Fischer- 344)	21d 6hr/d	Hepatic		400 (hypertrophy)		Odum et al. 1988	
			Renal	400				
68	Rat (Fischer- 344)	28d 6hr/d	Hepatic		200 (hypertrophy)		Odum et al. 1988	
			Renal	400				
69	Rat CFY	Gd 1-20 8 hr/d	Bd Wt	221 F		664 F (37% decreased body weight gain)	Szakmary et al. 1997	
70	Rat (Long- Evans)	6 hrs/day; 2 wks pre-mating-matii (5d/wk) and GD1-20	Hepatic		1000 F (increased relative maternal liver weight)		Tepe et al. 1980	
			Bd Wt	1000 F				
71	Rat (Long- Evans)	GD1-20 (6 hrs/day)	Hepatic		1000 F (increased relative maternal liver weight)		Tepe et al. 1980	
			Bd Wt	1000 F				

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
72	Rat (Alpk:APfSD)	19wk:11 wk, 5d/wk 6hr/d; daily during mating/lacta	Hepatic	1000			Tinston 1995	
			Renal	300 M	1000 M (minimal chronic progressive glomerulonephropathy; increased pleomorphism within proximal tubular nuclei)			
			Bd Wt	1000				
73	Mouse (B6C3F1)	28d 6hr/d	Renal	400			Green et al. 1990	
74	Mouse (Hybrid)	13 wk 5 d/wk 6 hr/d	Hepatic	265	609 (central enlargement of liver)		JISA 1993	
			Renal	265	609 (changes in proximal tubules)			
			Bd Wt	265 M	609 M (decreased body weight gain)			
75	Mouse (NMRI)	30 d 24hr/d	Hepatic		9 (liver enlargement and vacuolization of hepatocytes)		Kjellstrand et al. 1984	
			Bd Wt	150				

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
76	Mouse (NS)	8 wk 6d/wk 4hr/d	Hepatic		200 F (fatty degeneration)		Kylin et al. 1965	
			Renal	200 F				
			Bd Wt	200 F				
77	Mouse (B6C3F1)	13wk 5d/wk 6hr/d	Hepatic	200		400 (centrilobular liver necrosis)	NTP 1986	
			Renal	100	200 (karyomegaly of renal tubular epithelial cells)			
			Bd Wt	1600				
78	Mouse (B6C3F1)	28d 6hr/d	Hepatic		200 (peroxisomal proliferation; fatty changes)		Odum et al. 1988	
			Renal	400				
79	Mouse (B6C3F1)	21d 6hr/d	Hepatic		400 (peroxisomal proliferation; fatty changes)		Odum et al. 1988	
			Renal	400				
Immuno/ Lymphoret								
80	Rat (Sprague-Dawley)	6 hrs/day, 5 days/wk. 4 weeks		1000 F			Boverhof et al. 2012	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Neurological								
81	Rat (Sprague-Dawley)	30 or 90 d			320 M (changes in the fatty acid composition of the brain)		Kyrklund et al. 1988, 1990	
82	Rat (Fischer- 344)	13 wks 5 d/wk 6 h/d		200	800 (Increased apmlitude of flash evoked potential peak N3)		Mattsson et al. 1998	
83	Rat (Alpk:APfSD)	19wk:11 wk, 5d/wk 6hr/d; daily during mating/lacta		300	1000 (decreased activity, reduced response to sound, increased salivation, piloerection)		Tinston 1995	
84	Rat (Sprague-Dawley)	4 or 12 wk		300 M	600 M (decreased brain weight; decrease in cytoskeletal proteins)		Wang et al. 1993	
85	Gerbil (Mongolian)	90 d 24hr/d			60 (decreased DNA levels in frontal cortex)		Karlsson et al. 1987	
86	Gerbil (Mongolian)	3 mo 24hr/d			60 (decreased DNA content in the frontal cerebral cortex)		Rosengren et al. 1986	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
Reproductive									
87	Rat (albino)	GD 0-18 (7 hrs/day)		500 F				NIOSH 1980	
88	Rat (albino)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 0-18		500 F				NIOSH 1980	
89	Rat (albino)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 6-18		500 F				NIOSH 1980	
90	Rat CFY	Gd 1-20 8 hr/d		221 F		664 F	(increased pre-implantation loss)	Szakmary et al. 1997	
91	Rat (Long- Evans)	6 hrs/day; 2 wks pre-mating-matii (5d/wk) and GD1-20		1000 F				Tepe et al. 1980	
92	Rat (Long- Evans)	GD1-20 (6 hrs/day)		1000 F				Tepe et al. 1980	
93	Rat (Alpk:APfSD)	19wk:11 wk, 5d/wk 6hr/d; daily during mating/lacta		300		1000	(significant reduction in the number of live born pups; decreased pup survival during lactation)	Tinston 1995	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
94	Rabbit (New Zealand)	GD 0-21 (7 hrs/day)		500 F			NIOSH 1980	
95	Rabbit (New Zealand)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 0-21		500 F			NIOSH 1980	
96	Rabbit (New Zealand)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 7-21		500 F			NIOSH 1980	
Developmental								
97	Rat (Long- Evans)	6 hrs/day; 2 wks pre-mating-mati (5d/wk) and GD1-20		1000			Manson et al. 1981	
98	Rat (Long- Evans)	6 hrs/day, 5 days/week for 2 weeks pre-mating - mating		1000			Manson et al. 1981	
99	Rat (Long- Evans)	GD1-GD20 (6 hrs/day)		1000			Manson et al. 1981	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
100	Rat (albino)	GD 0-18 (7 hrs/day)		500					NIOSH 1980	
101	Rat (albino)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 0-18		500					NIOSH 1980	
102	Rat (albino)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 6-18		500					NIOSH 1980	
103	Rat CFY	Gd 1-20 8 hr/d		221			664	(increased percentage fetuses with growth retardation and malformations)	Szakmary et al. 1997	
104	Rat (Long- Evans)	6 hrs/day; 2 wks pre-mating-matii (5d/wk) and GD1-20			1000	(decreased fetal body weight; increased skeletal anomalies)			Tepe et al. 1980	
105	Rat (Long- Evans)	GD1-20 (6 hrs/day)			1000	(decreased fetal weight; increased soft tissue anomalies)			Tepe et al. 1980	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
106	Rat (Long- Evans)	6 hrs/day, 5 d/wk, 2 wks pre-mating-matii		1000			Tepe et al. 1980	
107	Rabbit (New Zealand)	GD 0-21 (7 hrs/day)		500			NIOSH 1980	
108	Rabbit (New Zealand)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 0-21		500			NIOSH 1980	
109	Rabbit (New Zealand)	7 hrs/day; 5 days/week for 3 weeks (pregestation) & GD 7-21		500			NIOSH 1980	
CHRONIC EXPOSURE								
Death								
110	Rat (Fischer- 344)	103wk 5d/wk 6hr/d				400 M (reduced survival)	Mennear et al. 1986; NTP 1986	
111	Rat (Sprague-Dawley)	6 hrs/day, 5 days/wk 12 months		300 M		600 M (increased mortality from 5th to 24th month of study attributed to chronic renal disease)	Rampy et al. 1978	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
112	Mouse (B6C3F1)	103wk 5d/wk 6hr/d				100 M (reduced survival)	Mennear et al. 1986; NTP 1986	
Systemic								
113	Human	20 yr average	Hepatic		15.8 (diffuse parenchymal changes revealed by ultrasound)		Brodkin et al. 1995	
114	Human	1-120 mo occup occup	Hemato	20			Cai et al. 1991	
			Hepatic	20				
			Renal	20				
115	Human	14 yr occup	Renal		10 (increased urine b-glucuronidase and lysozyme)		Franchini et al. 1983	
116	Human	6 yr occup	Hepatic	21			Lauwerys et al. 1983	
			Renal	21				
117	Human	10 yr average occup occup	Renal		15 (nephrotoxicity)		Mutti et al. 1992	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
118	Human	12 yr average occup	Renal	14			Solet and Robins 1991	
119	Human	9yr occup	Renal		23 F (increased urinary lysozyme activity)		Vyskocil et al. 1990	
120	Rat (Fischer- 344)	104 wk 5 d/wk 6 hr/d	Hepatic		200 (spongiosis hepatitis in males and increased alanine aminotransferase in females)		JISA 1993	
			Renal	50 M	200 M (increased relative kidney weight; nuclear enlargement of proximal tubules)			
			Bd Wt	50 F	200 F (reduced body weight)			

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
121	Rat (Fischer- 344)	103wk 5d/wk 6hr/d	Resp		200 thrombosis; squamous metaplasia of nasal cavity		Mennear et al. 1986; NTP 1986	
			Gastro	200 M	400 M forestomach ulcers			
			Renal		200 renal tubular karyomegaly			
			Endocr		200 M (adrenal medullary hyperplasia)			
			Bd Wt	400				
122	Rat (Sprague-Dawley)	6 hrs/day, 5 days/wk 12 months	Hemato	600			Rampy et al. 1978	
			Hepatic	600				
			Renal	600				
			Bd Wt	600				

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
123	Mouse (Hybrid)	104 wk 5 d/wk 6 hr/d	Hepatic	10 M	50 M (angiectasis and increased serum aspartate aminotransferase and alanine aminotransferase)		JISA 1993	
			Renal	50	250 (nuclear enlargement and atypical dilation of proximal tubules)			
124	Mouse (B6C3F1)	103wk 5d/wk 6hr/d	Resp		100 (acute passive congestion of the lungs)		Mennear et al. 1986; NTP 1986	
			Hepatic		100 hepatocellular degeneration			
			Renal		100 nephrosis			
			Bd Wt	200				
Neurological								
125	Human	1-30 yr		0.2			Altmann et al. 1995	
126	Human			0.2			Altmann et al. 1995	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
127	Human	1-120 mo occup occup			20 (increase in subjective symptoms including dizziness)		Cai et al. 1991	
128	Human	106 mo average			7.3[b] F (color vision loss)		Cavalleri et al. 1994	
129	Human	10 yr occup			15 F (increased reaction times)		Ferroni et al. 1992	
130	Human	6 yr occup		21			Lauwerys et al. 1983	
131	Human	occup occup		15.3 M			Nakatsuka et al. 1992	
132	Human			15.3 M			Nakatsuka et al. 1992	
133	Human	5.8 yr (mean)			0.11 (decreased visual contrast sensitivity)		Schreiber et al. 2002	
134	Human	4.0 yr (mean)			0.32 F (decreased visual contrast sensitivity)		Schreiber et al. 2002	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
135	Human	10 yr (mean)			0.05 (decreased visual contrast sensitivity)		Storm et al. 2011	
136	Gerbil (Mongolian)	12 mo 24hr/d			120 M (phospholipid changes in the cerebral cortex and hippocampus)		Kyrklund et al. 1984	
Cancer								
137	Rat (Fischer- 344)	104 wk 5 d/wk 6 hr/d				600 M (CEL: monocytic leukemia of spleen)	JISA 1993	
138	Rat (Fischer- 344)	103wk 5d/wk 6hr/d				200 (CEL: mononuclear cell leukemia)	Mennear et al. 1986; NTP 1986	
139	Mouse (Hybrid)	104 wk 5 d/wk 6 hr/d				250 (CEL: hepatocellular adenomas and carcinomas)	JISA 1993	

Table 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
140	Mouse (B6C3F1)	103wk 5d/wk 6hr/d				100 (CEL: hepatocellular carcinoma)	Mennear et al. 1986; NTP 1986	

a The number corresponds to entries in Figure 3-1.

b Used to derive a chronic-duration inhalation minimal risk level (MRL) of 0.006 ppm for tetrachloroethylene; the MRL was derived by converting the LOAEL of 7.3 ppm to an equivalent continuous exposure of 1.7 ppm and dividing by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability) and modifying factor of 3 for database deficiencies. ATSDR has adopted the chronic-duration inhalation MRL as the acute-duration and intermediate-duration inhalation MRLs. See Appendix A for detailed discussion of the inhalation MRLs for tetrachloroethylene.

ad lib = ad libitum; ALT = alanine aminotransferase; B = both sexes; Bd Wt = body weight; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); EEG = electroencephalogram; Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Metab = metabolism; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Occup = occupational; Pmd = pre-mating day; Pnd = post-natal day; Ppd = post-parturition day; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation

Acute (≤14 days)

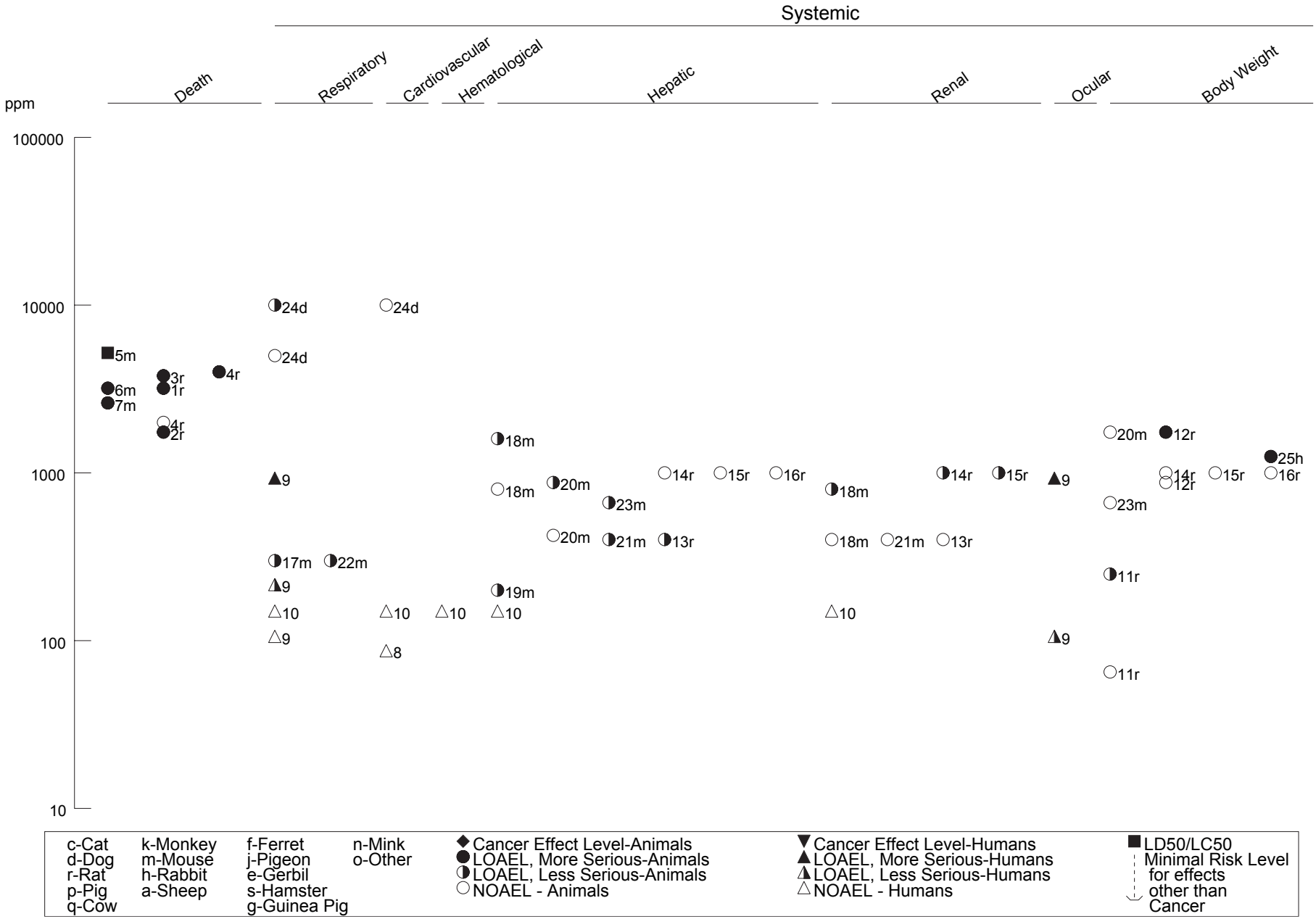


Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation *(Continued)*

Acute (≤14 days)

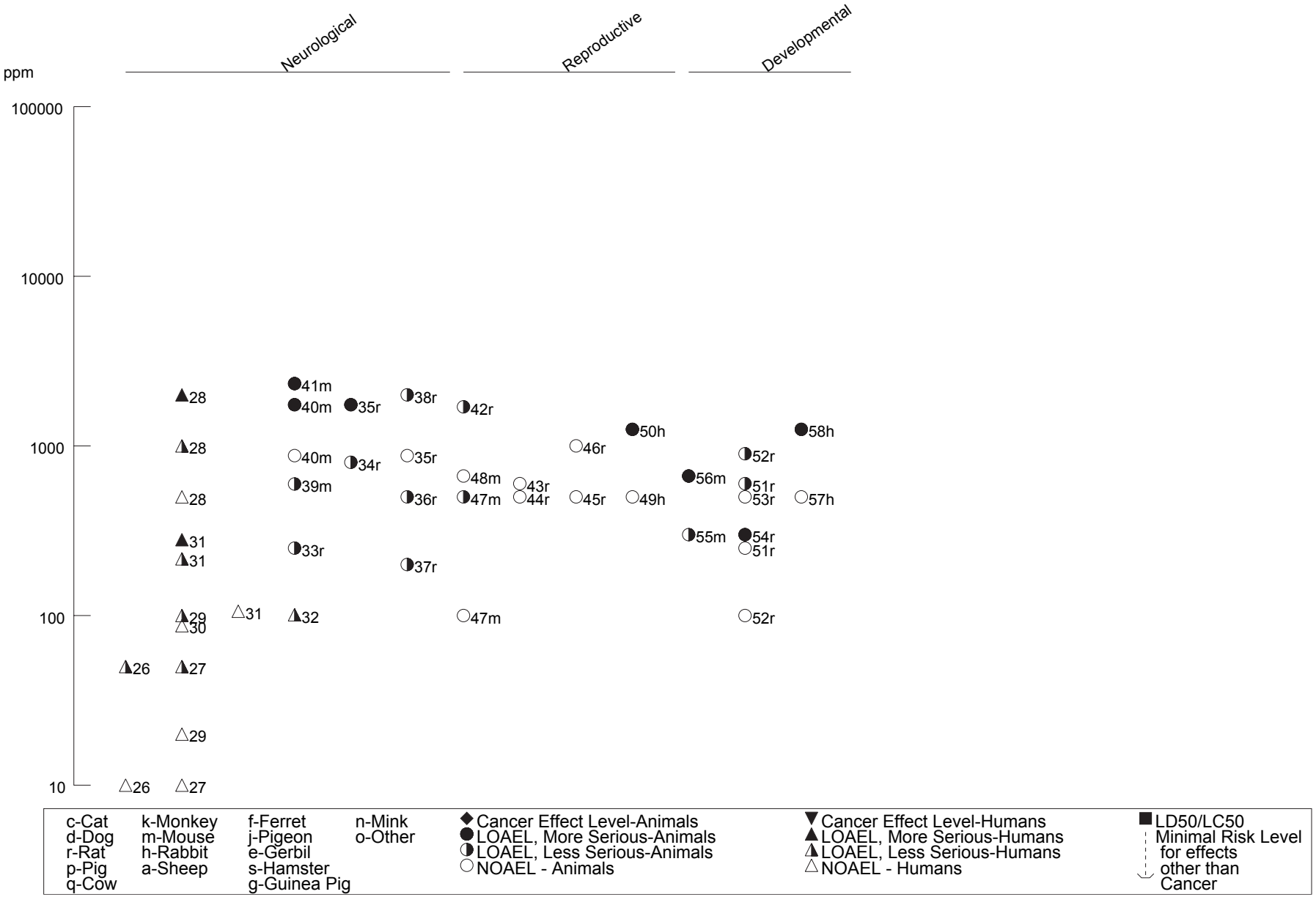


Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation *(Continued)*

Intermediate (15-364 days)

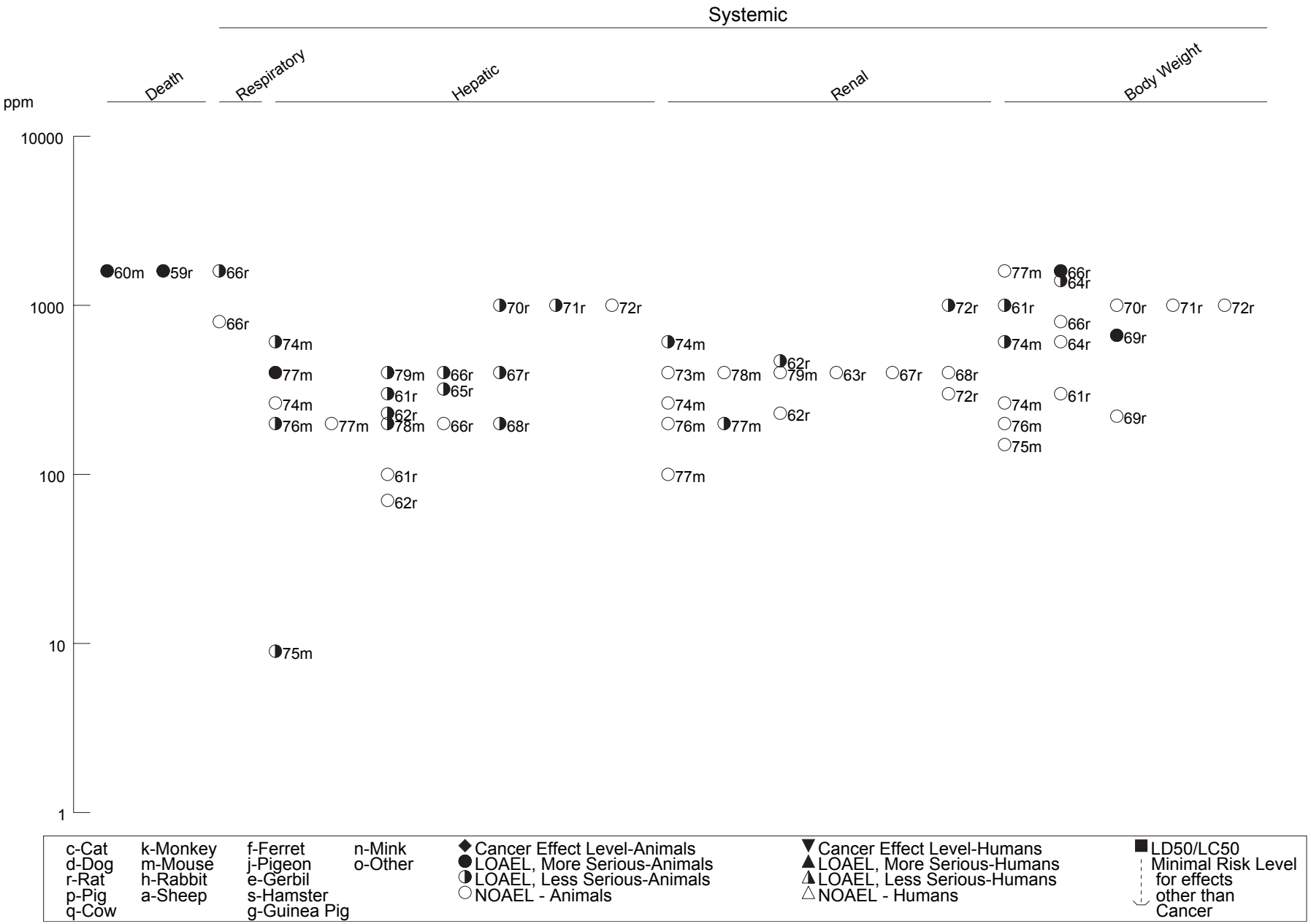


Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation *(Continued)*

Intermediate (15-364 days)

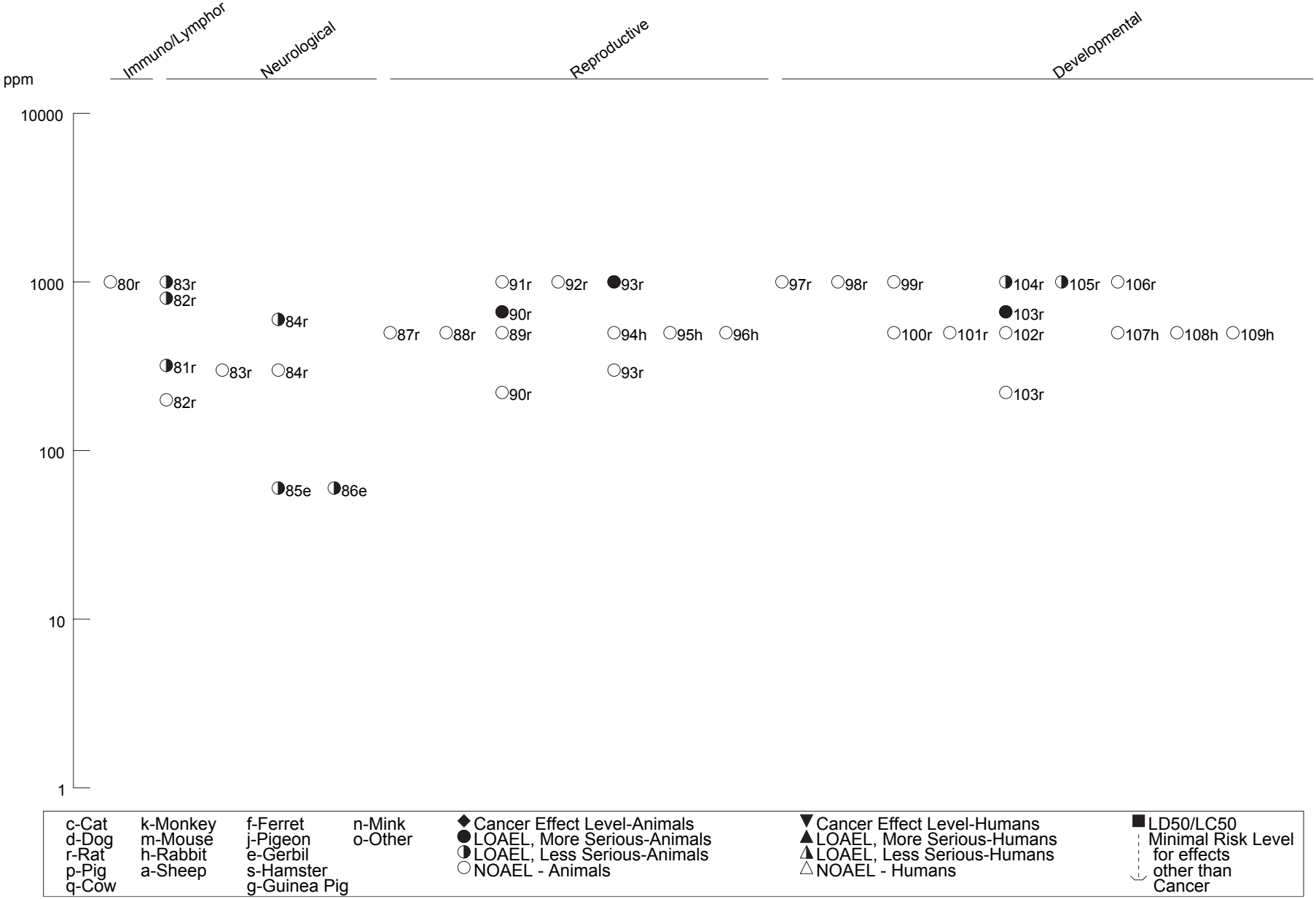
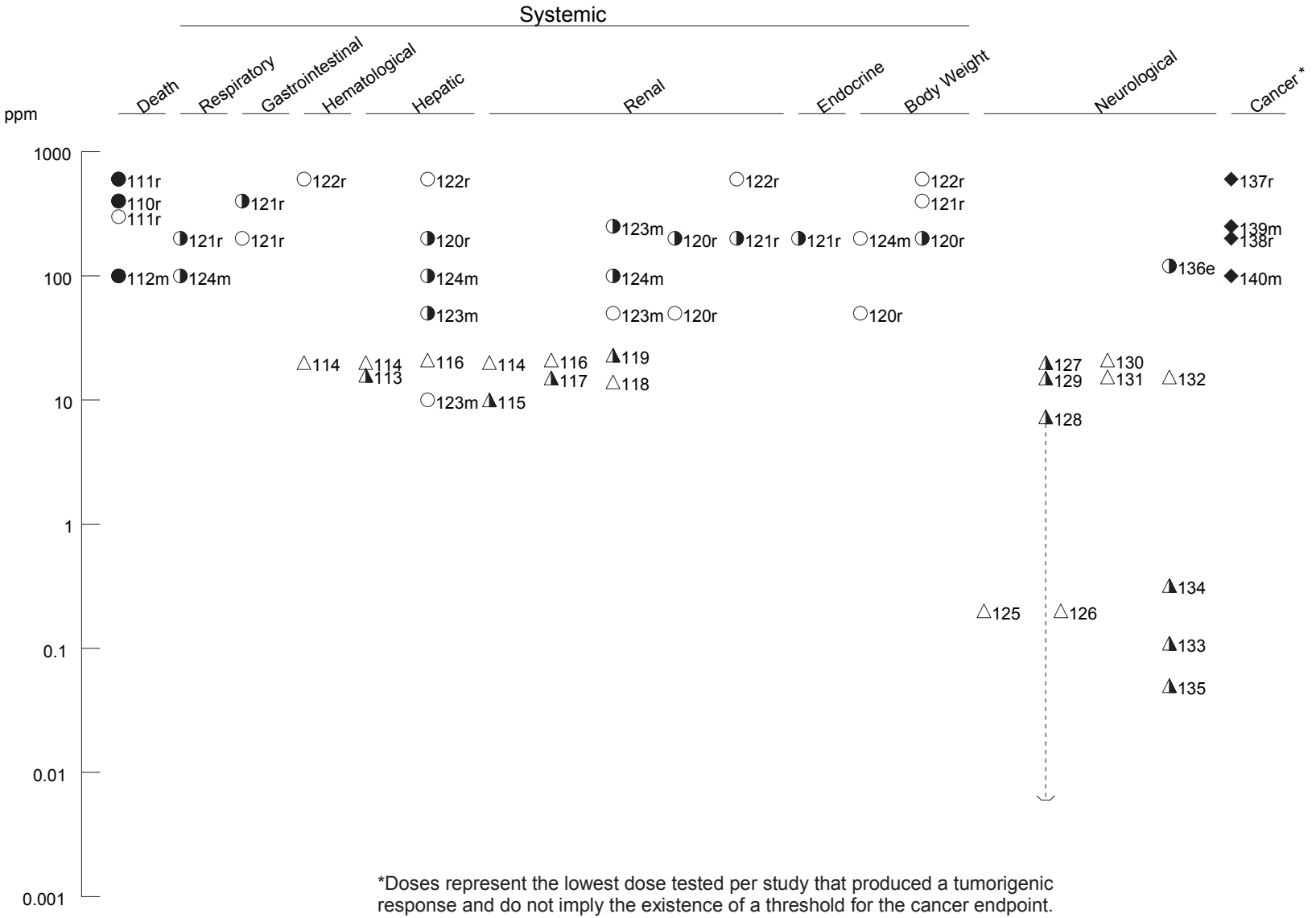


Figure 3-1 Levels of Significant Exposure to Tetrachloroethylene - Inhalation *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	k-Monkey	f-Ferret	n-Mink
d-Dog	m-Mouse	j-Pigeon	o-Other
r-Rat	h-Rabbit	e-Gerbil	
p-Pig	a-Sheep	s-Hamster	
q-Cow		g-Guinea Pig	

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

concentrations showed irritation of the respiratory tract at concentrations as low as 216 ppm for 2 hours (Rowe et al. 1952), with intense or unbearable irritation at concentrations ≥1,000 ppm, but no effects on pulmonary function at exposures up to 150 ppm, 7 hours/day for 5 days Carpenter 1937; Rowe et al. 1952). Other case reports that lacked information on exposure levels and duration (Patel et al. 1973; Tanios et al. 2004;) reported respiratory hypersensitivity and pulmonary edema in humans exposed to tetrachloroethylene. In animal studies, nasal lesions were observed in mice exposed to 300 ppm for 5 days (Aoki et al. 1994; Suzaki et al. 1997) and in rats exposed to ≥200 ppm for 2 years (Mennear et al. 1986; NTP 1986). Pulmonary congestion was seen in rats exposed to 1,600 ppm for 13 weeks and in mice exposed intermittently to concentrations ≥100 ppm for 2 years (Mennear et al. 1986; NTP 1986).

Intense irritation of the upper respiratory tract was reported in volunteers exposed to high concentrations (>1,000 ppm) of tetrachloroethylene (Carpenter 1937; Rowe et al. 1952). These older acute inhalation studies in humans were limited by small numbers of experimental volunteer subjects, incomplete characterization of subjects, variable concentrations of tetrachloroethylene, and reliance on self-reported symptoms, which are subjective. Respiratory irritation (irritation of the nasal passages) was reported in workers exposed to tetrachloroethylene vapors at levels of 232–385 ppm in a degreasing operation (Coler and Rossmiller 1953) and in volunteers exposed to concentrations as low as 216 ppm for 45 minutes to 2 hours (Rowe et al. 1952). Volunteers exposed to concentrations as high as 1,060 ppm could tolerate no more than 1–2 minutes of exposure before leaving the chamber (Rowe et al. 1952).

An experimental human exposure study titled *Tetrachloroethylene: Development of a biologic standard for the industrial worker by breath analysis*, completed by Stewart and colleagues, was first published by NIOSH in 1974. This publication can now be obtained from the National Technical Information Service (NTIS) with a 1981 date, and is cited as Stewart et al. (1981) throughout this Profile. In this study, four male volunteers were sequentially exposed to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 7.5 hours/day, 5 days/week (Stewart et al. 1981). The men were exposed to each concentration for 1 week. Once each week, pulmonary function was assessed at both rest and during two levels of exercise with forced maximum expiratory flow measurements, while alveolar-capillary gas exchange was measured by single breath carbon monoxide diffusion. The exposures to tetrachloroethylene at these vapor concentrations and time intervals had no effect on the pulmonary function measurements.

Case reports suggest possible pulmonary effects of exposure to tetrachloroethylene, but do not contain exposure information. A case report of hypersensitivity pneumonitis attributed the condition to tetrachloroethylene exposure; the woman worked as a dry cleaner (Tanios et al. 2004, see also

Section 3.2.1.3). Her symptoms included exertion-related dyspnea and a cough; CT scan of her chest showed a ground glass pattern and poorly defined parenchymal nodules. Bronchoalveolar lavage analysis indicated lymphocytosis. The investigators diagnosed the case as hypersensitivity pneumonitis related to tetrachloroethylene exposure. Pulmonary edema occurred in a 21-year-old male laundry worker after exposure to tetrachloroethylene vapors in a distilling operation; he became comatose shortly after exposure and was diagnosed with pulmonary edema after his rescue and admission to the hospital (Patel et al. 1973).

In a study designed to examine the effects of tetrachloroethylene on the respiratory mucosa, epithelial degeneration was observed in mice exposed to tetrachloroethylene at 300 ppm for 6 hours/day for 5 days (Aoki et al. 1994). The degeneration was more severe in the olfactory mucosa compared to other sites in the respiratory mucosa. Dilation of Bowman's glands and atrophy of olfactory nerves were also observed.

Male mice exposed to 300 ppm tetrachloroethylene for 6 hours/day on 5 days exhibited nasal discharge containing exfoliated epithelial cells and neutrophils, as well as lesions consisting of mucosal erosions in the olfactory region and inflammatory cell infiltration in the olfactory epithelium 2 weeks after exposure (Suzaki et al. 1997). Few changes were noted in the respiratory epithelium. In mice examined 1, 2, and 3 months after exposure, histopathological examination revealed evidence of repair of the olfactory mucosa; however, some of the olfactory epithelium was replaced by ciliated epithelium, and atrophy of the olfactory nerves and Bowman’s glands were noted (Suzaki et al. 1997).

Congestion of the lungs was reported in rats exposed intermittently to tetrachloroethylene at 1,600 ppm, but not 800 ppm, for 13 weeks (NTP 1986). Thrombosis and squamous metaplasia were observed in the nasal cavity of rats exposed intermittently at ≥200 ppm for 103 weeks (Mennear et al. 1986; NTP 1986). In mice exposed intermittently to tetrachloroethylene at ≥100 ppm for 103 weeks, acute passive congestion of the lungs was observed (Mennear et al. 1986; NTP 1986).

Cardiovascular Effects. Few studies have examined cardiovascular effects of tetrachloroethylene in humans or animals. Three acute duration experimental studies reported no effects on heart rate, blood pressure, and/or electrocardiograms in volunteers exposed to concentrations up to 150 ppm for up to 5 days (Ogata et al. 1971; Stewart et al. 1977, 1981). A case report of cardiac arrhythmia in a male dry cleaning worker did not report exposure concentrations, but did report a plasma concentration of 3.8 ppm tetrachloroethylene (Abedin et al. 1980). The only animal study of cardiovascular effects (Reinhardt et al.

1973) did not observe epinephrine-induced cardiac arrhythmia in beagle dogs exposed to concentrations up to 10,000 ppm.

No effects on heart rate or blood pressure were noted in four men exposed to tetrachloroethylene at 87 ppm for 3 hours (Ogata et al. 1971). Ten adult male volunteers and 10 adult female volunteers were exposed to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 1, 3, or 7.5 hours/day, 5 days/week for 1 week at each concentration (Stewart et al. 1981). During the exposure periods, blood pressure and pulse rate were measured every hour, while electrocardiograms were monitored continuously via telemetry. There was no deviation from the baseline measurements that were obtained preexposure or for the postexposure follow-up period (Stewart et al. 1981). These observations confirmed those of a separate study of six males and six females in which no effects on the electrical activity of the heart were observed following random exposure at 0, 25, and 100 ppm tetrachloroethylene vapor for 5.5 hours/day, 5 days/week (Stewart et al. 1977). The total study lasted 11 weeks, although the exposure concentrations varied daily throughout the study. A case report describes a 24-year-old man who experienced cardiac arrhythmia (frequent premature ventricular beats). The patient had been employed for 7 months in a dry cleaning facility where he used tetrachloroethylene (Abedin et al. 1980). Plasma tetrachloroethylene was measured at 0.15 ppm on his 5th day of hospitalization. The patient was discharged the next day, but returned in 2 weeks for outpatient evaluation with a recurrence of skipping of heartbeats, headache, and dizziness. At that time, plasma tetrachloroethylene was measured at 3.8 ppm. Since the biological exposure index associated with an 8-hour exposure of 25 ppm is 0.5 mg/L tetrachloroethylene in blood (ACGIH 2012), this subject was exposed to relatively high concentrations. The patient was reported to be asymptomatic 1 month after finding different employment (Abedin et al. 1980).

Epinephrine-induced cardiac arrhythmia was not induced in beagle dogs (5 and 12 dogs at the low and high exposure levels, respectively) exposed for 10 minutes by face mask to 5,000 or 10,000 ppm tetrachloroethylene (Reinhardt et al. 1973). This study was complicated by the dogs' struggling, which could represent irritant effects of these high tetrachloroethylene concentrations on the upper respiratory tract.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to tetrachloroethylene. Forestomach ulcers were observed in male rats exposed intermittently to tetrachloroethylene at 400 ppm for 103 weeks (NTP 1986). Ulcers were not observed at 200 ppm.

Hematological Effects. Available data provide suggestive, but not conclusive, information on potential hematologic effects of inhalation exposure to tetrachloroethylene; an experimental study observed no change from baseline hematology parameters after exposure to concentrations up to 150 ppm (Stewart et al. 1977, 1981), while a study of Egyptian dry cleaners exposed to <140 ppm tetrachloroethylene suggested decrements in hemoglobin and red blood cell count compared with an unexposed referent group (Emara et al. 2010). Limited animal data do not provide support for the findings in humans. Boverhof et al. (2012) observed no changes in hematology parameters in rats exposed to concentrations up to 1,000 ppm for 4 weeks, while a chronic cancer bioassay (JISA 1993) observed only increased mean corpuscular hemoglobin concentration (MCHC) in rats and gender-specific effects in mice.

Controlled human exposure studies of effects on complete blood count have not shown any change from preexposure values after exposures of adult male and female volunteers (6–10 per sex) to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 1, 3, or 7.5 hours/day, 5 days/week for 1 week at each vapor concentration (Stewart et al. 1981) or to 0, 25, or 100 ppm tetrachloroethylene vapor for 5.5 hours/day, 5 days/week, over an 11-week period (Stewart et al. 1977).

In contrast to the volunteer data, one epidemiological study (Emara et al. 2010) observed changes in selected hematology parameters among men employed as dry cleaners in Egypt; an earlier study (Cai et al. 1991) did not provide support for these findings. Emara et al. (2010) observed significantly ($p<0.05$) decreased hemoglobin, red blood cell counts, and mean cell hemoglobin concentration in male dry cleaner employees when compared with age- and lifestyle-matched unexposed referent subjects (n=40/group; 20 smokers, 20 nonsmokers). Mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were not affected by exposure. Average tetrachloroethylene exposure levels of <140 ppm were estimated from measurements made at various sites in each shop (Emara et al. 2010). No changes in hemoglobin concentration, red or white blood cell count, or hematocrit were observed in Chinese dry cleaning workers (29 men and 27 women) exposed to tetrachloroethylene at a geometric mean time-weighted average (TWA) concentration of 20 ppm, when compared with unexposed controls (30 men and 35 women) (Cai et al. 1991).

In animals, intermediate-duration studies of exposure up to 1,000 ppm have not suggested effects of tetrachloroethylene on hematology. Hematology end points (including hemoglobin, hematocrit, red cell and reticulocyte counts, total and differential white cell counts, and platelet counts) were not affected in

female Sprague-Dawley rats at the end of 4 weeks of exposure to tetrachloroethylene vapors 6 hours/day, 5 days/week at concentrations of 0, 100, 300, or 1,000 ppm (Boverhof et al. 2012). A dose-dependent decrease in erythrocyte δ-aminolevulinate dehydratase activity, which is necessary for heme production, was observed in rats exposed to 200 and 600 ppm, but not 50 ppm, tetrachloroethylene for 4 weeks (Soni et al. 1990). It is not clear if exposure was intermittent or continuous. A transient increase in reticulocytes was observed in mice exposed to tetrachloroethylene at 135 and 270 ppm during the first few weeks of an 11.5-week study (Seidel et al. 1992). Microscopic examination of bone marrow revealed no effect on pluripotent stem cells and only a small reduction in erythroid committed cells. Because of a lack of statistical analysis, NOAELs and LOAELs were not clearly identified in the Seidel et al. (1992) study. Rats exposed to 230 or 470 ppm tetrachloroethylene for up to 160 days exhibited splenic congestion and increased hemosiderin deposits (Carpenter 1937); however, the study is limited by the use of sick animals (parasites, pneumonia), nonstandard study protocols, rats of undefined strain, and inadequate controls.

In a chronic cancer bioassay (JISA 1993), hematology changes observed at sacrifice of Crj:BDF1 mice after 104 weeks of exposure to 250 ppm tetrachloroethylene (the highest concentration tested) included increased red blood cells and hematocrit, increased hemoglobin (females only) and reduced MCV, MCH, and MCHC (males). In the corresponding rat study (JISA 1993), the only hematology change noted was an increase in mean corpuscular hemoglobin in female rats exposed to 600 ppm (the highest concentration tested).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to tetrachloroethylene. Histological changes were not observed in the limb muscles of rats exposed to tetrachloroethylene at 50, 200, or 800 ppm 6 hours/day, 5 days/week for 13 weeks (Mattsson et al. 1992, 1998).

Hepatic Effects

Hepatic Effects in Humans. The liver may be a target organ in humans exposed to tetrachloroethylene. Case reports (Coler and Rossmiller 1953; Hake and Stewart 1977; Meckler and Phelps 1966; Saland 1967; Stewart et al. 1961a) have documented liver injury consisting of hepatomegaly, icterus, and clinical chemistry changes in exposed humans, but no information on exposure concentrations was available. Controlled, acute-duration human exposure studies (Stewart et al. 1977, 1981) using concentrations up to 150 ppm tetrachloroethylene have not shown effects on serum levels of hepatic enzymes. However,

studies of occupationally-exposed individuals have provided suggestive evidence for subclinical liver effects (changes in GGT isozyme fractions and diffuse parenchymal changes seen on ultrasound) in humans exposed chronically to lower levels (10–20 ppm TWA) of tetrachloroethylene (Brodkin et al. 1995; Gennari et al. 1992). Other serum markers for liver function were not altered at these exposure levels (Brodkin et al. 1995; Cai et al. 1991; Lauwerys et al. 1983).

Hepatocellular damage was documented by biopsy in a case study of a woman exposed occupationally to tetrachloroethylene fumes for 2.5 months (Meckler and Phelps 1966). Liver damage also has been diagnosed in exposed individuals by the presence of hepatomegaly, icterus, and elevations of serum glutamic oxaloacetic transaminase (SGOT), bilirubin, and urinary urobilinogen (Coler and Rossmiller 1953; Hake and Stewart 1977; Saland 1967; Stewart et al. 1961a). These effects were generally observed several days after acute exposure to concentrations that resulted in nervous system effects. There was one case report of diffuse fatty liver in a dry cleaner who died shortly after being exposed to tetrachloroethylene fumes (Levine et al. 1981). Because of the brief interval between exposure and death, this liver lesion may have been preexistent.

Ten adult male volunteers and 10 adult female volunteers were sequentially exposed to 0, 20, 100, or 150 ppm tetrachloroethylene vapor for 1, 3, or 7.5 hours/day, 5 days/week for 1 week at each exposure concentration (Stewart et al. 1981). No ethanol consumption was permitted during the exposure sequence. A complete panel of clinical chemistries including serum alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT), SGOT, and serum bilirubin was obtained each week. These results were compared to the preexposure values; no deviation from baseline was observed (Stewart et al. 1981). Similarly, when six males and six females were randomly exposed to 0, 25, or 100 ppm tetrachloroethylene vapor for 5.5 hours/day, 5 days/week, over an 11-week period, no deviations from baseline values were observed in weekly blood samples analyzed for serum alkaline phosphatase, SGPT, SGOT, and serum bilirubin (Stewart et al. 1977).

In two studies assessing hepatic enzyme levels in serum of dry cleaners exposed to TWA concentrations of ~20 ppm tetrachloroethylene, no evidence of increased enzyme levels including SGOT, SGPT, and alkaline phosphatase was noted (Cai et al. 1991; Lauwerys et al. 1983). However, subtle differences in the isoenzyme fractionation of serum gamma-glutamyltransferase (GGT) enzymes were observed in 141 workers exposed to tetrachloroethylene at an average concentration of 11.3 ppm relative to 130 unexposed controls (Gennari et al. 1992). Both exposed and control subjects were chosen on the basis of normal liver function tests (SGOT, SGPT, serum alkaline phosphatase, lactate dehydrogenase

[LDH], and 5'-nucleotidase). In exposed workers, total GGT was significantly (1.4-fold; $p<0.01$) increased, principally as a result of an increase in GGT-2. Small amounts of GGT-4 were only observed in exposed workers. No correlation between serum GGT levels and worker tetrachloroethylene exposure level or duration was found. The investigators indicated that GGT-4 is associated with hepato-biliary impairment and that further investigation is required to determine why low-level exposure to tetrachloroethylene is associated with changes in the GGT isoenzyme profile in workers without any other evidence of liver disease.

Changes in serum levels of liver enzymes may not be the most sensitive marker of liver effects following exposure to tetrachloroethylene, as an ultrasound study suggested morphological changes in the absence of elevated serum enzymes. In dry cleaning workers exposed to an average of 15.8 ppm tetrachloro-ethylene for 20 years, ultrasound revealed diffuse parenchymal changes in the livers of 18/27 (67%) exposed compared with 10/26 (38%; significantly different at $p<0.05$) unexposed laundry workers (Brodkin et al. 1995). An exposure-related trend was also noted, with parenchymal changes observed in all 5 subjects with exposures >15 ppm, in 6 of the 12 subjects with exposures <15 ppm, and in 10/26 (38%) unexposed laundry workers. No changes in serum markers of liver damage (SGOT, SGPT, GGT, alkaline phosphatase, and total and direct bilirubin) were noted in these workers (Brodkin et al. 1995). The mean age and duration of employment of the exposed and control groups differed significantly (average age of exposed subjects was 46 years, compared with 38 years in controls, and exposed subjects had worked an average of 15 years longer than controls), limiting the conclusions that can be drawn from this study.

Hepatic Effects in Animals. Hepatic lesions are clearly shown in experimental animals during inhalation exposure to tetrachloroethylene. Mice are more sensitive to this effect than rats, as demonstrated in studies of acute, intermediate, and chronic duration. The lowest LOAELs for hepatic effects in animals exposed for acute, intermediate, and chronic durations are 200 ppm (mice; Kylin et al. 1963), 9 ppm (mice; Kjellstrand et al. 1984), and 50 ppm (mice; JISA 1993). Chronic exposure of mice to tetrachloroethylene results in heptaocellular adenomas and carcinomas, while these tumor types are not increased by exposure of rats (JISA 1993; NTP 1986). Section 3.2.1.7 provides additional details of the liver cancer data on tetrachloroethylene.

The available acute-duration inhalation studies demonstrate liver effects in mice exposed to concentrations as low as 200 ppm, while rats appear to be resistant to hepatotoxic effects even at concentrations more than 10-fold higher. Hepatocellular vacuolization occurred after a single 4-hour

exposure of mice to ≥200 ppm concentrations of tetrachloroethylene (Kylin et al. 1963). This lesion was also reported in 4/5 male B6C3F1 mice exposed to 875 ppm and in all male and female mice exposed to 1,750 ppm tetrachloroethylene for 14 days; vacuolization was not present at 425 ppm (NTP 1986). In another 14-day study, JISA (1993) observed fading of the liver at necropsy of mice exposed to ≥400 ppm, along with "central enlargement" of the liver at the highest concentration (1,600 ppm); no additional details were provided. Liver lesions were not observed in rats exposed for 14 days to concentrations up to 1,750 ppm in the study by NTP (1986) or up to 3,200 ppm in the study by JISA (1993).

The type of liver lesions differs markedly between mice and rats after intermediate- and chronic-duration exposures to tetrachloroethylene. Mice develop vacuolization, peroxisome proliferation, necrosis, and, with prolonged exposure, neoplasia; effects in rats appear to be less severe, consisting of centrilobular hypertrophy and hyperplasia. In a study correlating light microscopic and ultrastructural liver effects with liver levels of cyanide-insensitive palmitoyl CoA oxidase, a marker for peroxisomal β-oxidation, peroxisome proliferation was observed in mice, but not in rats (Odum et al. 1988). Animals were exposed to 200 ppm of tetrachloroethylene for 28 days or 400 ppm for 14, 21, or 28 days. Centrilobular hepatocellular vacuolization was induced in mice by tetrachloroethylene exposure. Electron microscopy revealed that this effect corresponded to lipid accumulation. Centrilobular hepatocytes with cytoplasmic eosinophilia on light microscopy had marked proliferation of cytoplasmic peroxisomes at the ultrastructural level, and there was a significant increase in the marker enzyme. These changes occurred in mice at both doses and all exposures and were most pronounced in male mice.

When NMRI mice were exposed to 0, 9, 37, 75, or 150 ppm tetrachloroethylene continuously for 30 days (Kjellstrand et al. 1984), exposed mice developed hepatocellular vacuolization and enlargement. Lesions were observed at 37 ppm and were noted to be most pronounced at exposures to 75 and 150 ppm; further details were not provided. Relative liver weights were not calculated; however, absolute liver weights were significantly elevated at all exposure concentrations and remained elevated 120 days following exposure to 150 ppm (Kjellstrand et al. 1984). In a 13-week study, male mice exposed to ≥200 ppm tetrachloroethylene exhibited mitotic alterations in the liver, while both sexes had leukocytic infiltrations, centrilobular necrosis, and bile stasis at ≥400 ppm (NTP 1986).

In contrast to the effects seen in mice in the study by Odum et al. (1988), which included vacuolization, lipid accumulation, and peroxisome proliferation, when rats were exposed to 200 ppm of tetrachloroethylene for 28 days or 400 ppm for 14, 21, or 28 days, male rats in both dose groups and female rats exposed to 400 ppm developed centrilobular hepatocellular hypertrophy (Odum et al. 1988).

Ultrastructural findings consisted of proliferation of smooth endoplasmic reticulum, with no increase in peroxisomes (Odum et al. 1988). Centrilobular hypertrophy was also the only liver lesion in female Sprague-Dawley rats exposed to tetrachloroethylene vapors at 0, 100, 300, or 1,000 ppm, 6 hours/day, 5 days/week for 4 weeks in an immunotoxicity study. Relative liver weight was significantly increased at 300 and 1,000 ppm (8 and 9% higher than controls, respectively) (Boverhof et al. 2012). Very slight hypertrophy of the centrilobular hepatocytes was observed in 4/8 rats exposed to 300 ppm and in 7/8 rats exposed to 1,000 ppm tetrachloroethylene; the control incidence was not reported (Boverhof et al. 2012).

Dose-related liver congestion was observed in rats exposed to tetrachloroethylene for 13 weeks, with 8/20, 10/20, and 15/19 rats affected at 400, 800, and 1,600 ppm tetrachloroethylene, respectively; no liver effects were observed at 200 ppm (NTP 1986). In a reproductive toxicity study, hepatic effects were not observed in parental male and female rats exposed to 1,000 ppm of tetrachloroethylene 6 hours/day, 5 days/week for 11–19 weeks (Tinston 1995).

Chronic inhalation bioassays of mice and rats confirm the sensitivity of mice to hepatic effects of tetrachloroethylene and the qualitative differences in the lesions induced in the two species. Hepatocellular degeneration and necrosis occurred in male mice exposed to 100 and 200 ppm tetrachloroethylene for 103 weeks and in females exposed to 200 ppm (NTP 1986). Similar effects were seen in another chronic bioassay of Crj:BDF1 mice; at ≥50 ppm, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were increased and angectasis was observed in the livers of males, and at 250 ppm, serum AST and ALT were increased and angectasis was observed in females; absolute and relative liver weight were increased and focal hepatocellular necrosis occurred in males; and central degeneration of the liver was seen in both sexes. Both sexes of mice also had increased incidences of hepatocellular tumors in both studies at exposure concentrations ≥100 ppm (JISA 1993; NTP 1986). Liver effects were not reported in rats exposed chronically to 200 or 400 ppm tetrachloroethylene in the study by NTP (1986), but the effects of mononuclear cell leukemia infiltrates may have obscured subtle compound-induced changes. The other available chronic bioassay (JISA 1993) reported increased serum ALT in female rats and spongiosis hepatitis in males exposed to ≥200 ppm. At 600 ppm (the highest concentration tested), serum ALT was increased in males, triglycerides were reduced in females, and the incidence of liver hyperplasia was increased in male rats. Unlike the mice, exposed rats did not exhibit an increased incidence of liver tumors in either study (JISA 1993; NTP 1986). These studies are discussed further in Section 3.2.1.7.

Renal Effects

Renal Effects in Humans. The kidney may also be affected in humans exposed to tetrachloroethylene, based on information provided in a case report of accidental exposure (Hake and Stewart 1977) and studies of dry cleaning workers exposed chronically to tetrachloroethylene (Bundschuh et al. 1993; Franchini et al. 1983; Mutti et al. 1992; Price et al. 1995; Verplanke et al. 1999; Vyskocil et al. 1990). Several studies of occupational populations suggest an association between tetrachloroethylene exposure to concentrations between 10 and 85 ppm and alterations in urinary and serum markers indicative of glomerular and/or tubular dysfunction (Franchini et al. 1983; Mutti et al. 1992; Vyskocil et al. 1990). These studies were generally of small populations (the largest was 82 subjects) with varying exposure durations, but measured sensitive indicators of renal function. Other studies measuring urinary proteins, *n*-acetyl-glucosaminidase (NAG), blood urea nitrogen (BUN), and serum creatinine have not shown effects at occupational exposure levels (Cai et al. 1991; Solet and Robins 1991). A retrospective cohort study showed an increased risk of hypertensive end-stage renal disease in dry cleaning workers exposed to tetrachloroethylene (Calvert et al. 2011).

Limited information is available on renal effects after acute-duration exposure of humans. Evidence of renal dysfunction, including proteinuria and hematuria, was reported in an individual after accidental exposure to anesthetic concentrations (exposure estimates were not reported, but the subject was unconscious) of tetrachloroethylene vapor (Hake and Stewart 1977). In acute-duration controlled human exposure studies, no changes from baseline levels of urinalysis parameters or BUN were observed after a 1-week exposure to concentrations up to 150 ppm for up to 7.5 hours/day (Stewart et al. 1981).

Assessment of urinary markers of renal damage in dry cleaning workers exposed to tetrachloroethylene in several studies has provided indicators of renal changes after chronic exposure to concentrations of 10–23 ppm (Franchini et al. 1983; Vyskocil et al. 1990). Workers in dry cleaning shops exposed for an average of 14 years to an estimated TWA concentration of 10 ppm of tetrachloroethylene had increased urinary levels of lysozyme and β-glucuronidase, suggestive of mild tubular damage (Franchini et al. 1983). Urinary lysozyme activity was also increased in workers exposed to an average of 23 ppm for about 9 years (Vyskocil et al. 1990). At unspecified exposure concentrations and durations, an increase in urinary fibronectin was observed in workers exposed to tetrachloroethylene (Bundschuh et al. 1993); no effects on urinary proteins (high and low molecular weight) or NAG were observed. No effects on BUN or serum creatinine were observed in workers exposed at an average concentration of 20 ppm for 1–

120 months (Cai et al. 1991), and occupational exposure to tetrachloroethylene at an average concentration of 14 ppm for an average of 12 years had no effects on total urinary protein, albumin, NAG, and creatinine (Solet and Robins 1991). In another report, serum creatinine and urinary albumin, β_2-microglobulin, and retinol-binding protein levels were normal in dry cleaning workers exposed to a TWA concentration of 21 ppm of tetrachloroethylene for 6 years (Lauwerys et al. 1983). Relative to age- and sex-matched unexposed controls, laminin fragments in the serum (n=37) and urine (n=50) of tetrachloroethylene-exposed workers were significantly increased, suggesting glomerular dysfunction (Price et al. 1995). The exposure concentrations and the duration of exposure were not stated.

In a more comprehensive examination of kidney function, 9 men and 41 women occupationally exposed to tetrachloroethylene from trace levels to 85 ppm were compared with 50 controls (Mutti et al. 1992). Exposure levels and parameters of kidney function were both measured over a long period of time to account for variability in the working cycle or seasonal fluctuations; however, the total duration of the study was not stated. The results showed an increase in markers suggesting an increase in the shedding of epithelial membrane components from tubular cells in the exposed group. The following urinary markers were increased in exposed workers relative to unexposed workers: fibronectin; albumin; transferrin; brush-border antigens BBA, BB50, and HF5; and tissue nonspecific alkaline phosphatase. Serum antiglomerular basement membrane antibodies and serum laminin levels were also significantly increased in exposed workers compared to controls. No effects on serum β_2-microglobulin, creatinine, or urinary prostaglandins, glycosaminoglycans, NAG, or intestinal alkaline phosphatase were noted. The investigators (Mutti et al. 1992) indicated that the significance of the findings was unclear, and they suggested that the changes could be a physiological adaptation to exposure or may represent an early state of potentially progressive renal disease.

A larger study of workers exposed to lower concentrations showed only subtle effects on urinary markers of renal function. Verplanke et al. (1999) measured urinary markers in dry cleaning employees (82 exposed and 19 unexposed) in the Netherlands, whose TWA exposure, as measured in alveolar air samples, was 8.4 mg/m^3 (1.2 ppm). The exposed and control groups did not differ significantly with respect to age, sex, body mass, percent of smokers, alcohol consumption, or duration of employment. No differences in urinary levels of NAG, β-galactosidase, alanine aminopeptidase, or albumin were observed; a significant increase in retinol binding protein (75.4 versus 41.6 µg/g creatinine in unexposed employees) was noted. The study authors reported that retinol binding protein is a more sensitive indicator of renal tubular dysfunction than NAG. Renal parameters did not correlate with exposure concentration or with a measure of cumulative dose that took into account concentration and exposure duration.

Calvert et al. (2011) observed a significantly elevated risk of hypertensive end-stage renal disease among 1,296 dry cleaning workers in four U.S. cities. The standardized incidence ratios (SIRs) were 1.98 (95% confidence interval [CI] 1.11–3.27) for the entire cohort and 2.88 (95% CI 1.15–5.23) in the subgroup exposed only to tetrachloroethylene (n=494).

Renal Effects in Animals. In animal studies, adverse renal effects have been observed in rodents exposed to tetrachloroethylene. Little information on renal effects after acute-duration exposure is available, but intermediate-duration studies have shown tubular histopathology, increased kidney weights, and glomerulonephropathy in rats, mice, and guinea pigs exposed to concentrations >400 ppm (Carpenter 1937; JISA 1993; Jonker et al. 1996; NTP 1986; Rowe et al. 1952; Tinston 1995). Both male and female mice and rats exhibited renal effects from exposure, but F344 rats appeared to be less susceptible than other strains. Similar nonneoplastic renal effects were observed in male and female rats (including F344 rats) and male and female mice in chronic studies using lower exposure concentrations (JISA 1993; NTP 1986)

An acute-duration study reported hyaline droplets in proximal tubules, but no tubular damage or cell proliferation occurred in male rats exposed to 1,000 ppm by inhalation for 10 days (Green et al. 1990). JISA (1993) reported few details of its 14-day studies in rats and mice, but indicated that mice exhibited necrosis and regeneration of the proximal tubules in both sexes exposed to ≥800 ppm tetrachloroethylene; no renal effects were reported in rats. In the 14-day study by NTP (1986), no renal histopathology changes were reported in rats or mice at exposure concentrations up to 1,750 ppm.

In intermediate-duration studies, high concentrations of tetrachloroethylene were associated with renal effects in rats, mice, and guinea pigs. Female Wistar rats exposed to 2,500 ppm tetrachloroethylene for 32 consecutive days exhibited increased urine volume; increased protein, GGT, ALP, LDH, and NAG excretion; increased relative kidney weight; and increased incidences of mild multifocal tubular vacuolation and karyomegaly in the kidneys (Jonker et al. 1996). Minimal chronic progressive glomerulonephropathy and increased pleomorphism within the proximal tubular nuclei were noted in male, but not female, Alpk:ApfSD rats exposed to tetrachloroethylene at 1,000 ppm for up to 19 weeks (6 hours/day, 5 days/week); no effects occurred at 300 ppm (Tinston 1995). Albino rats of unspecified strain exposed to 470 ppm for 150 days or to 7,000 ppm for ≥40 exposures exhibited intratubular casts and swelling and desquamation of tubular epithelium (Carpenter 1937). Available studies in F344 rats show few or no renal effects. Kidney lesions did not occur in F344 rats exposed to 1,600 ppm on

6 hours/day, 5 days/week for 13 weeks; kidneys from lower dose groups were not examined microscopically (NTP 1986). Likewise, the JISA (1993) 13-week study reported no renal findings in male or female F344DuCrj rats exposed to concentrations up to 1,400 ppm; however, the study authors reported "sporadic" urinalysis changes in both sexes of rat at exposures ≥609 ppm. It is not clear whether the differences in renal toxicity stem from strain specificity or differences in the exposure regimens.

At concentrations of ≤400 ppm, few renal changes were seen in rats of any strain. Intermittent exposure of Sprague-Dawley rats to 200 ppm tetrachloroethylene for 4 weeks induced renal P-450 enzymes (Soni et al. 1990); other end points of renal function were not assessed. Neither abnormal renal function nor histopathological findings were observed in Wistar-derived rats exposed to tetrachloroethylene vapor concentrations of 0, 100, 200, or 400 ppm for about 6 months (Rowe et al. 1952). Peroxisomal proliferation was not induced in renal tubular epithelium of F344 rats or B6C3F1 mice exposed to 200 or 400 ppm tetrachloroethylene for up to 28 days (Odum et al. 1988). Male rats F344 rats exposed to 400 ppm tetrachloroethylene for 28 days did not develop kidney lesions (Green et al. 1990).

Few data on kidney effects are available in mice exposed for intermediate durations; these studies suggest that renal changes can occur at concentrations of ≥600 ppm for 13 weeks. Renal tubular karyomegaly (nuclear enlargement) occurred in 7/10 male and 7/10 female B6C3F1 mice exposed to 1,600 ppm tetrachloroethylene for 13 weeks (NTP 1986). Renal effects were not seen at 100 ppm; kidneys of the remaining exposure groups (200, 400, and 800 ppm) were not examined microscopically. JISA (1993) reported no urinalysis alterations in Crj:BDF1 mice, but indicated that concentrations of ≥609 ppm resulted in changes in the renal proximal tubules (further details were not provided).

Guinea pigs that received 18 exposures of 7 hours each to 2,500 ppm tetrachloroethylene over a period of 20 days had increased kidney weights with slight-to-moderate cloudy swelling of tubular epithelium (Rowe et al. 1952). Neither abnormal renal function nor histopathological findings were observed in guinea pigs exposed to tetrachloroethylene vapor concentrations of 0, 100, 200, or 400 ppm for about 6 months (Rowe et al. 1952).

Chronic bioassays indicate similar types of nonneoplastic renal effects in rats and mice at comparable exposure concentrations. In the NTP (1986) chronic inhalation toxicity/oncogenicity study of tetrachloroethylene, F344 rats of each sex were exposed to 0, 200, or 400 ppm tetrachloroethylene, and B6C3F1 mice were exposed to 0, 100, or 200 ppm tetrachloroethylene for 103 weeks. Dose-related increases in the incidence of renal tubular cell karyomegaly occurred in both species and sexes at all

exposure concentrations. The highest incidences were seen in male rats (37/49 and 47/50 at 200 and 400 ppm, compared with 1/49 controls) and male mice (17/49 and 46/60 at 100 and 200 ppm, compared with 4/49 controls). This alteration was accompanied by low incidences of renal tubular cell hyperplasia and increased incidences of tubular cell adenoma or adenocarcinoma in male rats, but not in female rats or in male or female mice (NTP 1986). JISA (1993) observed increased absolute and relative kidney weights in male and relative kidney weights in female F344 rats exposed to ≥200 ppm tetrachloroethylene for 104 weeks, nuclear enlargement of proximal tubules of the kidneys at ≥200 ppm in males and at 600 ppm in females, atypical tubular dilation of the proximal tubules and exacerbation of chronic renal disease in males at 600 ppm. In Crj:BDF1 mice exposed for 104 weeks in the bioassay conducted by JISA (1993), nuclear enlargement of proximal tubules of the kidneys was noted in males and females exposed to 250 ppm (the highest concentration tested), and atypical tubular dilation of the proximal tubules occurred at this concentration in females.

Endocrine Effects. Few studies in humans or animals have examined endocrine effects of tetrachloroethylene exposure. Data are limited to a study of prolactin levels in humans exposed occupationally (Ferroni et al. 1992) and histopathology examination of the pituitary glands in rats exposed for 13 weeks (Mattsson et al. 1992, 1998) or adrenal glands in rats and mice exposed for 2 years (JISA 1993; NTP 1986). Cortical and medullary hyperplasia of the adrenal glands is the only adverse effect noted in the available studies.

Ferroni et al. (1992) measured prolactin levels in 30 controls and in 60 women occupationally exposed to tetrachloroethylene at a median concentration of 15 ppm. Although they noted a significant increase in prolactin levels in the exposed women relative to the controls during the proliferative phase of the menstrual cycle, values of both groups were in the normal range. Therefore, it is unlikely that the effect observed in this population has biological significance.

Treatment-related histological changes were not observed in the pituitaries of rats exposed to tetrachloroethylene at 50, 200, or 800 ppm 6 hours/day, 5 days/week for 13 weeks (Mattsson et al. 1992, 1998) or in rats or mice exposed to concentrations up to 250 ppm for 2 years (JISA 1993; NTP 1986). Medullary hyperplasia of the adrenal glands was observed in male rats at both exposure levels (5/49, 14/49, and 24/49 at 0 [control], 200, and 400 ppm respectively), and increased incidence of cortical hyperplasia of the adrenal glands was observed in female rats at the high exposure (4/50, 6/49, and 11/47 at 0 [control], 200, and 400 ppm respectively), when both groups were exposed to tetrachloroethylene for

103 weeks (NTP 1986). Adrenal glands were not affected in mice in the chronic bioassay by NTP (1986) or in mice or rats in the bioassay reported by JISA (1993).

Ocular Effects. Ocular effects of tetrachloroethylene in humans include irritation and vision decrements. Effects on vision, including impairments in color vision and contrast discrimination, have been reported in people exposed to low levels of tetrachloroethylene (0.02–15 ppm) occupationally or through residing in buildings with co-located dry cleaners (Cavalleri et al. 1994; Gobba et al. 1998; Schreiber et al. 2002; Storm et al. 2011). Because this effect may be a neurological effect rather than a direct action on the eyes, it is discussed in more detail in Section 3.2.1.4.

Intense irritation of the eyes of humans was noted following acute exposure to high concentrations (930 ppm) of tetrachloroethylene vapors (Carpenter 1937; Rowe et al. 1952). Burning or stinging sensations in the eyes occurred after exposure to 600 or 280 ppm; very mild irritation was reported by four subjects at exposure to 216 or 106 ppm (Rowe et al. 1952); and transient eye irritation was noted in six subjects during the first few minutes of exposure at 75–80 ppm (Stewart et al. 1961b). The Rowe et al. (1952) and Carpenter (1937) studies are limited by small numbers of subjects, variable concentrations of tetrachloroethylene, and lack of measured clinical changes. Onofrj et al. (1999) reported acute optic neuritis in a 57-year-old female dry cleaner after 9 hours of ironing; her exposure during this activity was estimated to be as high as 64–252 ppm (see details in Section 3.2.1.4).

Histological changes were not observed in the eyes of rats exposed to tetrachloroethylene at 50, 200, or 800 ppm 6 hours/day, 5 days/week for 13 weeks (Mattsson et al. 1992, 1998).

Body Weight Effects. No studies of body weight effects in humans exposed to tetrachloroethylene were identified in the available literature. In studies in laboratory animals, body weights were decreased in rats exposed to ≥1,750 ppm and in mice exposed to 3,200 ppm for 2 weeks (JISA 1993; NTP 1986). Studies of intermediate-duration exposures also showed body weight decrements at high (>1,000 ppm) concentrations in rats, mice, and guinea pigs (JISA 1993; NTP 1986; Rowe et al. 1952); however, the findings are not consistent across studies of the same species. Reduced body weights were observed in rats and mice exposed to ≥200 ppm in one of two chronic bioassays (JISA 1993) but not in the other (NTP 1986).

Following intermittent exposure to tetrachloroethylene for 2 weeks, body weights of rats but not mice were significantly reduced at 1,750 ppm (NTP 1986). JISA (1993) indicated that rats and mice treated for

2 weeks with exposure to tetrachloroethylene concentrations up to 3,200 ppm exhibited decreased body weight gain, but did not indicate the effective concentrations or magnitude of change. Pregnant CD rats exposed to concentrations of 250 or 600 ppm tetrachloroethylene for 6 hours/day on gestation days 6–19 exhibited decreased body weight gain (19% less than controls at both exposures) during gestation days 6–9; body weight gain did not differ from controls for the remainder of the exposure duration (Carney et al. 2006).

Following intermediate-duration exposure to tetrachloroethylene, body weights of rats were significantly reduced at 1,400 ppm (JISA 1993) or 1,600 ppm (NTP 1986); no body weight changes greater than 10% were noted in rats exposed at 800 ppm (Mattsson et al. 1992, 1998) or 1,000 ppm (Tinston 1995). No effects on body weight were noted in mice intermittently exposed to tetrachloroethylene for intermediate durations at concentrations as high as 1,600 ppm (Kjellstrand et al. 1985; Kylin et al. 1965; NTP 1986); however, decreased body weight gain was reported in male mice exposed to ≥609 ppm and female mice exposed to 1,400 ppm in the 13-week study by JISA (1993). Guinea pigs exposed to tetrachloroethylene at 2,500 ppm for 24 days lost weight, and female guinea pigs exposed to 200 ppm 7 hours/day for 158 exposures in 220 days showed a significantly lower (18% lower than air-exposed controls, p=0.011) final body weight (Rowe et al. 1952). Limitations of this study include the use of small numbers of animals and intercurrent infection.

Body weight effects were not observed in rats exposed to tetrachloroethylene at 400 ppm or in mice exposed at 200 ppm for 103 weeks (NTP 1986). However, male rats exposed to 600 ppm, female rats exposed to ≥200 ppm, and male and female mice exposed to 250 ppm tetrachloroethylene for 2 years exhibited body weight decrements (magnitude of changes was not reported) throughout most of the exposure period in the chronic bioassay by JISA (1993).

3.2.1.3 Immunological and Lymphoreticular Effects

The available studies of immunological effects in humans exposed to tetrachloroethylene provide suggestive evidence for alterations in blood biomarkers related to inflammation and hypersensitivity; however, the data are limited and exposure concentrations are uncertain. The only study explicitly examining immune system effects in animals exposed to tetrachloroethylene via inhalation was a 4-week study that observed no immune system effects in rats at concentrations up to 1,000 ppm (Boverhof et al. 2012).

Emara et al. (2010) observed increased serum and cellular IL-4 levels and serum IgE levels, potentially indicative of enhanced hypersensitivity responses, in Egyptian dry cleaners. Hematological parameters (see Section 3.2.1.3), serum immunoglobulin levels, and cytokine levels were measured in groups of male dry cleaner employees and age- and lifestyle-matched unexposed referent subjects (n=40/group; 20 smokers, 20 nonsmokers). Average tetrachloroethylene exposure levels of <140 ppm were estimated from five vapor concentration measurements obtained by sampling various sites in each shop; details of the sampling and analysis methods were not provided. Blood tetrachloroethylene levels in nonsmoking unexposed subjects, smoking unexposed subjects, nonsmoking workers, and smoking workers were measured to be 0.11, 0.11, 1,681, and 1,695 μg/L, respectively. Serum and cellular IL-4 levels and serum IgE levels were significantly increased in both smoking and nonsmoking workers, compared to their respective referent groups. No significant change was found in serum or cellular IFN-γ levels or serum IgA, IgM, or IgG levels. In a study examining a wide variety of VOCs, Lehmann et al. (2002) reported decreased percentages of IFN-γ-producing T cells in the umbilical cord blood of infants (total n=85) from homes with higher levels of tetrachloroethylene (>7.3 $\mu g/m^3$ or 0.001 ppm, the 75th percentile concentration) compared with infants from homes with lower levels (less than the 75th percentile); the odds ratio (OR; adjusted for family atopy history, gender, and maternal smoking during pregnancy) for reduced percentage of IFN-γ-producing T cells was 2.9 (95% CI 1.0–8.6). In addition, the crude data on percentages of cytokine-producing T cells suggested decreases in TNF-α- and IL-2-producing cells associated with exposure to tetrachloroethylene at concentrations above the 75th percentile. Levels of 28 VOCs in the homes were measured by continuous passive air sampling during 4 weeks after birth. This study is limited by the fact that exposure measurements occurred after the measurement of outcome (cord blood cytokine-producing T-cells), and indoor levels of tetrachloroethylene likely vary over time based on the presence or absence of recently dry-cleaned materials in the home. In addition, the analyses did not account for potential confounding by coexposure to other VOCs. Thus, the association between indoor tetrachloroethylene and cytokine-producing T-cells in neonates is uncertain.

The limited available epidemiological studies investigating allergic sensitization and asthma have not observed a clear role for tetrachloroethylene exposure in the development of these conditions, but a case report of hypersensitivity pneumonitis provides some support. Lehmann et al. (2001) measured indoor concentrations of several VOCs in the bedrooms of 3-year-old children and assessed their association with serum IgE antibodies to food, indoor, and outdoor allergens. The 25th, 50th, and 75th percentile concentrations of tetrachloroethylene were 0.87, 2.54, and 5.09 $\mu g/m^3$, respectively. While there were significant associations between some VOCs and sensitization to food allergens (eggs or milk), there was not a significant association between indoor tetrachloroethylene levels and food allergies. Further, there

was no evidence for increased indoor (e.g., pet) or outdoor (e.g., pollen) allergen sensitization with higher levels of any VOC (Lehmann et al. 2001). In a small group of Hispanic children with asthma in Los Angeles, the daily severity of asthma symptoms was not correlated with the current ambient air levels of tetrachloroethylene or the amount of tetrachloroethylene in expired air (Delfino et al. 2003); limitations of this study include small sample size and lack of full participation at each measurement timepoint. A case report of hypersensitivity pneumonitis attributed the condition to tetrachloroethylene exposure; the woman worked at a dry cleaner (Tanios et al. 2004, see also Section 3.2.1.2). Other potential causes and diagnoses were ruled out by CT of her chest, blood chemistry, and analysis of bronchoalveolar lavage.

Andrys et al. (1997) reported statistically significant alterations in a number of blood immunological parameters when 21 dry cleaning workers were compared with measurements from a referent group of 16 "administrators" or when compared with laboratory reference values (LRVs). However, all of the measurements from the exposed group were within the normal range of the LRVs, and multiple parameters from the control group were outside the normal range of the LRVs, limiting the conclusions that can be drawn from the findings. When a small group of highly exposed subjects (n=6) were analyzed separately and the results were compared with LRVs, significant increases in total leucocyte numbers, lysozymes, circulating immunocomplexes, number of phagocytosing cells in peripheral blood, α2-macroglobulin levels, and C4 complement components were noted, as were decreased prealbumin concentrations. However, the small number of highly exposed subjects limits the interpretation of these findings.

A 4-week rat study of immunotoxicity (Boverhof et al. 2012) observed no evidence for effects on a wide range of immune system end points. No changes in white blood cell counts; the number of cells, protein levels, or amount of lactate dehydrogenase in the bronchoalveolar lavage fluid; the phagocytic activity of pulmonary alveolar macrophages; the splenic antibody forming cell (AFC) response to sheep red blood cells (SRBCs); or weights or histopathology of immune system organs (spleen or thymus) were observed in female Sprague-Dawley rats exposed to tetrachloroethylene vapors at 0, 100, 300, or 1,000 ppm, 6 hours/day, 5 days/week for 4 weeks (Boverhof et al. 2012).

In a mouse study (see the discussion of respiratory effects in Section 3.2.1.2), there was increased host susceptibility to pulmonary bacterial infection after a 3-hour inhalation exposure to 50 ppm tetrachloroethylene (Aranyi et al. 1986). The specific mechanism of the increased susceptibility is unknown. The significance of the study is unclear because of variability in control group mortality and lack of evaluation of specific immunological end points.

A chronic study of rats exposed to tetrachloroethylene for 104 weeks (JISA 1993) observed no changes in spleen weight or histopathology of thymus or lymph nodes at concentrations up to 600 ppm; increased incidences of mononuclear leukemia of the spleen were noted (see Section 3.2.1.7). The study authors reported that male mice, but not female mice exposed to 250 ppm tetrachloroethylene for 104 weeks exhibited increased absolute and relative spleen weight (data were not shown; JISA 1993). No histopathology changes of the spleen, thymus, or lymph nodes were reported.

3.2.1.4 Neurological Effects

Neurological Effects in Humans. The nervous system is a major target organ in humans exposed to tetrachloroethylene by inhalation. Acute exposure, depending on concentration, can result in electrophysiological changes, reversible mood and behavioral changes, impairment of coordination, or anesthetic effects. Studies in humans exposed for years in occupational or residential settings have suggested effects on color vision and visual contrast sensitivity, as well as additional neurobehavioral effects. There are no studies of humans exposed to tetrachloroethylene for intermediate durations of time.

Acute-Duration Neurological Effects in Humans. Volunteers exposed to tetrachloroethylene for short periods of time have reported symptoms of lightheadedness, dizziness, and loss of coordination at concentrations between 100 and 300 ppm for <2 hours or 600 ppm for 10 minutes (Carpenter 1937; Rowe et al. 1952; Stewart et al. 1961b). Symptoms of neurological impairment were not reported after exposure to 106 ppm for 1 hour (Rowe et al. 1952). Slight lightheadedness was reported by six male volunteers exposed to tetrachloroethylene at a concentration of 210–240 ppm for over 30 minutes (Stewart et al. 1961b). Symptoms of dizziness and drowsiness were reported at exposure to 216 ppm for 45 minutes to 2 hours; loss of motor coordination occurred at exposure to 280 ppm for 2 hours or 600 ppm for 10 minutes (Rowe et al. 1952). In an older study, mood changes, slight ataxia, faintness, and dizziness occurred with exposure to concentrations of 1,000–1,500 ppm for <2 hours (Carpenter 1937). With exposure to 2,000 ppm for 5–7 minutes, subjects experienced a sensation of impending collapse (Carpenter 1937). Dizziness has also been reported after brief accidental exposure to high concentrations of tetrachloroethylene fumes (Saland 1967), while longer exposures resulted in collapse, coma, and seizures (Hake and Stewart 1977; Morgan 1969; Patel et al. 1973; Stewart 1969; Stewart et al. 1961a).

In contrast to the lack of symptoms reported in humans exposed to 106 ppm for 1 hour (Rowe et al. 1952), exposure to 100 ppm for 7 hours produced symptoms such as headache, dizziness, difficulty in

speaking, and sleepiness (Stewart et al. 1970). Of five objective tests of central nervous system performance in humans exposed to 100 ppm for 7 hours/day on 5 consecutive days, none showed any abnormality except the Romberg test of balance, which was abnormal for three of the five subjects; no control subjects were included in this study (Stewart et al. 1970). Hake and Stewart (1977) reported impaired coordination, as measured by the Flanagan coordination test, at some time points during exposure of four male volunteers to 100 or 150 ppm tetrachloroethylene for 7.5 hours/day for 5 days.

Electrophysiological changes, including EEG alterations and changes in visual-evoked potentials, have been noted in studies of volunteers exposed for up to 5 days to tetrachloroethylene concentrations in the range of 50–100 ppm. EEGs of volunteers exposed to tetrachloroethylene show evidence of central nervous system depression at concentrations of ≥100 ppm. Subjective evaluation of electroencephalographic scores suggested cortical depression in male volunteers exposed to 100 ppm for 7.5 hours/day for 5 days, but not when the same individuals were exposed to 20 ppm (Hake and Stewart 1977). In a later investigation a larger group of 19 volunteers (10 males and 9 females) was exposed 5 days/week to tetrachloroethylene vapor concentrations of 0, 20, 100, or 150 ppm for 1, 3, or 7.5 hours/day (subjects were exposed to each concentration for 1 week) (Stewart et al. 1981). Major changes were observed in the EEG of three of four male subjects and four of five female subjects after exposure to 100 ppm. In the majority of subjects, the EEG changes were characterized by a reduction in overall wave amplitude and frequency, most strikingly evident in the occipital leads; the EEG alterations were similar to those seen in healthy adults during drowsiness, light sleep, and the first stages of anesthesia (Stewart et al. 1981).

Altmann et al. (1990) found a statistically significant ($p<0.05$) increase in latency of pattern reversal visual-evoked potentials in 10 male volunteers exposed to tetrachloroethylene at 50 ppm for 4 hours/day for 4 days, relative to 12 subjects exposed at 10 ppm. No effects on brainstem auditory-evoked potentials were noted. A second study completed by Altmann et al. (1992) confirmed the effect on pattern reversal visual-evoked potentials at 50 ppm and the lack of effect on brainstem auditory-evoked potentials when 16 male volunteers were exposed 4 hours/day for 4 days and compared with a group exposed to 10 ppm. No effects on flash visual-evoked responses were noted in male volunteers exposed for 5 days, 7.5 hours/day to concentrations up to 150 ppm tetrachloroethylene (Hake and Stewart 1977). The lack of effect on flash visual-evoked potentials in the Hake and Stewart (1977) study may reflect the greater inter- and intrasubject variability of waveforms for flash visual-evoked potentials (Otto et al. 1988).

Altmann et al. (1992) completed a battery of neurological tests including finger tapping; eye-hand coordination using a sine wave tracking task; simple reaction time; continuous performance test; symbol-

digit test; visual retention; pattern recognition; digit learning; paired associates learning and retention; vocabulary test; and mood scales. Analysis of covariance, with preexposure baseline values as covariates, revealed significant performance deficits for vigilance (p=0.04) and eye-hand coordination (p=0.05) at 50 ppm. A borderline (p=0.09) effect on simple reaction times was also noted at 50 ppm. No effects on math skills, time discrimination, or reaction times were noted in male volunteers exposed for 5 days, 7.5 hours/day to concentrations up to 150 ppm tetrachloroethylene (Hake and Stewart 1977).

A case report described the acute onset of optic neuritis in a 57-year-old female dry cleaner (Onofrj et al. 1999). Symptoms of headache, retroorbital pain, and loss of vision other than light perception occurred after the subject had spent 9 hours ironing freshly dry-cleaned clothes and fabrics. Her visual field was markedly restricted, consisting of a "tunnel vision" effect that persisted during the 1 year follow-up time. While ambient measurements of tetrachloroethylene had been within exposure limits (25–50 ppm) when tested biannually, testing conducted to simulate the conditions that she experienced while ironing revealed concentrations as high as 64 and 252 ppm near the newly cleaned fabrics and in the steam from the iron (respectively), suggesting that her exposure prior to the incident may have been much higher. Other potential causes of optic neuritis were ruled out, and blood samples collected 2 days after symptom onset showed 1.08 mg/g tetrachloroethylene, leading the authors to suggest exposure as the cause of the optic neuritis (Onofrj et al. 1999). While the subject of this case report was employed in dry cleaning and was thus likely exposed to tetrachloroethylene for a number of years, it appears that the acute, high concentration exposure may have triggered the optic neuritis.

Intermediate-Duration Neurological Effects in Humans. There are no studies of neurological effects in humans exposed for intermediate durations.

Chronic-Duration Neurological Effects in Humans. Studies in dry cleaners suggest that chronic exposure to tetrachloroethylene may result in neurological symptoms and effects on memory, concentration, and reaction time that could persist after cessation of exposure. In a study of 26 dry cleaning workers (primarily women) in Belgium exposed to a TWA concentration of 21 ppm tetrachloroethylene over an average of 6 years, no significant alterations were detected in the overall prevalence of neurological symptoms or in tests of psychomotor performance compared to 33 unexposed controls (Lauwerys et al. 1983). However, 17 of 22 subjective neurologic symptoms were more prevalent in the exposed group, particularly memory loss (7/26 versus 3/33 controls) and difficulty in falling asleep (11/26 versus 6/33 controls). Exposure assessment included measurement of urinary trichloroacetic acid daily for 1 week, measurement of air tetrachloroethylene concentrations with personal air samplers and badges, and

measurement of breath and blood concentrations of tetrachloroethylene. Cai et al. (1991) also reported an increase in subjective symptoms including dizziness and forgetfulness in workers exposed to tetrachloroethylene at a geometric mean concentration of 20 ppm for 1–120 months relative to unexposed controls. Gregersen (1988) observed persistent symptoms of memory loss and poor concentration among workers who had been free of organic solvent exposure for 6.6 years; however, this study combined workers with exposure to tetrachloroethylene with those exposed to other solvents, so it is not clear whether the persistent changes are attributable to tetrachloroethylene exposure.

Chronic-duration effects on neurobehavioral function: Three studies examining neurobehavioral function in dry cleaning workers (Echeverria et al. 1995; Seeber 1989) or people residing above or near dry cleaning facilities (Altmann et al. 1995) showed impairments in tasks associated with memory, attention, and reaction time. These studies have suggested a possible effect of chronic tetrachloroethylene exposure on the functioning of the frontal lobes (mediating complex organizational behavior, attention executive functioning, and reasoning) and the limbic system (mediating mood and memory). Benignus et al. (2009) reported a meta-analysis of these three studies, and observed a higher magnitude of effect (normalized across the three studies and tests applied) with the lower estimated cumulative exposure in the residential study than with the higher occupational exposures. The authors postulated a series of potential explanations for this finding, including the possibility that the findings of low-level residential effects were related to an effect of acute exposure (e.g., resulting from the exposure in the home during the day(s) prior to testing), which may not have existed in occupational groups tested after several hours or up to 2 days without exposure. Other possible explanations suggested by the authors included: (1) the potential greater susceptibility of residents compared with workers, due to the "healthy-worker" effect or due to differences in age or gender between the two populations; and (2) differences in exposure scenario (i.e., residents are exposed to lower concentrations but more continuously and over longer periods than workers, and workers' time away from work provides greater opportunity for elimination of tetrachloroethylene from the body).

In a study of 65 dry cleaning workers exposed to tetrachloroethylene for at least 1 year, behavioral tests that measured short-term memory for visual designs showed deficits in the high-exposure group (40.8 ppm) relative to the low-exposure group (11.2 ppm) (Echeverria et al. 1995). Exposure was assessed by a breath sample, and by 15-minute air samples from the breathing zone of a clerk, a pressor, and an operator in 19 of the 23 shops studied; exposure groups (low, medium, and high) were then created based on work history. These authors (Echeverria et al. 1995) also described four cases referred for neuropsychologic assessment of possible tetrachloroethylene encephalopathy. The subjects performed

below expectation on tasks assessing memory, motor, visuospatial, and executive functions, with milder attentional deficits.

Dry cleaning workers exposed to a TWA concentration of 12 or 54 ppm tetrachloroethylene had significantly impaired perceptual function, attention, and intellectual function compared to a control population when evaluated by a battery of psychological tests and questionnaires (Seeber 1989). The workers were exposed on average 12 and 11 years in the low- and high-exposure groups, respectively (as reported by U.S. EPA 2012a). The study showed statistically significant differences, indicative of impairment, between exposed and control groups in test scores for neurological signs, emotional lability, perceptual speed, delayed reactions, digit reproduction, cancellation d2 (fault corrected performance), and digit symbol, after controlling for gender, age, and intelligence. Among these tests, only scores for perceptual speed, delayed reactions, and digit reproduction exhibited monotonic dose-response relationships; for the other tests, the scores were worse in the low exposure group than in the high-exposure group (Seeber 1989). Compared to 30 unexposed women, significantly prolonged reaction times (simple reaction times, $p<0.0001$; shape comparison to test vigilance and to test stress, $p<0.005$) were reported in 60 women occupationally exposed to tetrachloroethylene at a median concentration of 15 ppm for an average of 10 years (Ferroni et al. 1992). Exposure levels were determined by measuring tetrachloroethylene in the blood collected during the workday and in air samples collected during 4-hour periods in the workweek. The sampling was completed during the winter and summer to account for seasonable variability. No significant association between measures of exposure and neurobehavioral tests was noted.

In a study comparing 14 persons living above or next to dry cleaning facilities for 1–30 years with 23 controls with no history of solvent exposure, no significant differences were observed in the absolute values of tests of a neurological battery (pattern reversal visual-evoked potentials continuous performance test, hand-eye coordination, finger tapping, simple reaction time, visual memory) (Altmann et al. 1995). However, when analyzed using multivariate analysis to adjust for age, gender, and education, response time in the continuous performance test and simple reaction time were increased ($p<0.05$), and a smaller number of stimuli were identified correctly by the exposed subjects ($p<0.05$) relative to 23 controls. The median concentrations of tetrachloroethylene were 0.2 and 0.003 ppm in the apartments of exposed and control subjects, respectively; blood concentrations measured in the examination room (not in the apartments) were 17.8±46.9 µg/L (mean±standard deviation) in exposed subjects and below the 0.5 µg/L detection limit in controls.

Chronic-duration effects on vision: Chronic tetrachloroethylene exposure may alter specific types of vision functions, including color discrimination and contrast sensitivity; however, the available data include some conflicting findings.

No effect on blue-yellow color vision (assessed using Lanthony's new color and Ishihara's color vision tests) was noted in 30 men or 34 women occupationally exposed to tetrachloroethylene at average concentrations of 15.3 and 10.7 ppm, respectively (Nakatsuka et al. 1992). The average duration of exposure for these subjects was not stated; in addition, details of the sampling for tetrachloroethylene concentrations were not provided.

When compared to 35 unexposed controls (matched for sex, age, alcohol consumption, and cigarette use), 22 dry cleaners exposed to an average concentration of 7.3 ppm tetrachloroethylene for an average of 106 months showed a significant decrease ($p=0.007$) in color vision, primarily in the blue-yellow range, as measured by the Lanthony D-15 desaturated panel (Cavalleri et al. 1994). Reexamination of the workers 2 years later showed that those workers whose exposure to tetrachloroethylene had increased (n=19, median exposure increasing from 1.7 to 4.3 ppm based on 4-hour TWA concentration measurements) experienced further decrements in color vision, while those whose exposure had decreased experienced no changes in color vision (n=14, median exposure decreasing from 2.9 to 0.7 ppm); two workers had retired and were not reexamined (Gobba et al. 1998). CCI, again measured using the Lanthony D-15 panel, was increased from 1.16 to 1.26 in the group with increased tetrachloroethylene exposure ($p<0.01$). In both the initial and follow-up studies, the exposure concentrations were measured on a single day; thus, it is not clear how well they represent long-term exposure. Gobba et al. (1998) noted that the Lanthony D-15 panel is a more sensitive test for early color vision loss than the tests used by Nakatsuka et al. (1992), and that the increased sensitivity might be one reason for the conflicting results obtained by Cavalleri et al. (1994) and Gobba et al. (1998) compared with Nakatsuka et al. (1992). Color discrimination (measured by Lanthony D-15 test) was not significantly affected in 4 children or 13 adults exposed to concentrations up to 0.3 ppm tetrachloroethylene for an average of 4–5 years; exposure resulted from living in residential buildings that also housed dry cleaning facilities (Schreiber et al. 2002). The mean color confusion index score of the exposed persons (1.33) was higher than that of age- and sex-matched controls (1.20), but the difference was not statistically significant by two-tailed matched-pair analysis (Schreiber et al. 2002).

Other studies that did not quantify exposure to tetrachloroethylene provide some support for effects on color vision. A study of 14 dry cleaning workers (7 men and 7 women) also observed poorer color

discrimination, primarily in the blue-yellow range, when compared with two referent groups (n=27 and 29) consisting of support staff of the investigating university (Sharanjeet-Kaur et al. 2004). Testing using the D-15 and Farnsworth Munsell 100 Hue tests indicated abnormal performance (based on criteria published by Vingrys and King-Smith 1988) among 43 or 93% (respectively) of dry cleaners, compared with 0% of each of the referent groups (statistical analysis was not performed). The authors suggested that the FM 100 Hue test was a more sensitive test for acquired color vision deficits (Sharanjeet-Kaur et al. 2004). The study is limited by the lack of matching in selection of the referent population and lack of control for potential confounders including age and smoking status. Till et al. (2003) compared the color vision and contrast sensitivity in a 30-month-old child whose mother worked as a dry cleaner prior to and during pregnancy with similar test results from three unexposed 2-year-old children. The exposed child exhibited severe red-green color vision deficit, and mild to moderate impairment of blue-yellow color vision (Till et al. 2003). Due to the age and limited language abilities of the children, testing was accomplished by measurement of transient and sweep visual-evoked potentials. Valic et al. (1997) examined color confusion in 138 individuals who reported exposure to solvents compared with 100 controls. The subjects included 31 individuals who reported exposure to trichloroethylene or tetrachloroethylene for an average of 5 years; urine levels of trichloroacetic acid were measured to validate exposure. Among those exposed to tri- or tetrachloroethylene in combination with ≥250 g of alcohol per week, the CCI (assessed by Lanthony D-15 test) was higher (1.80) than in those subjects whose alcohol intake was similar but who were not exposed to the chlorinated solvents. Among those without alcohol intake, exposure did not affect CCI. Urinary trichloroacetic acid levels were not correlated with CCI (Valic et al. 1997).

Tetrachloroethylene exposure may also alter visual contrast sensitivity. In one volunteer study that evaluated this end point, tests of visual contrast measured in a few individuals showed a tendency for loss of contrast in the low and intermediate spatial frequencies after exposure to 50 ppm on 4 hours/day for 4 days (Altmann et al. 1990). Two epidemiological studies of exposure to tetrachloroethylene from living or working in buildings that also housed dry cleaners (Schreiber et al. 2002; Storm et al. 2011) suggested that exposure to concentrations of 0.1–0.3 ppm could alter visual contrast sensitivity in adults, and that this end point might be affected at lower concentrations in children. Schreiber et al. (2002) evaluated a group of residents (n=17) and a group of daycare workers (n=9), each of whom was exposed to tetrachloroethylene for an average of 4 or 5.8 years (respectively) originating from a dry cleaner that was colocated with the residence or daycare. Visual acuity, color discrimination, and contrast sensitivity were assessed in these groups and in age- and sex-matched controls without exposure. Ambient and personal air monitoring results suggested mean concentrations of about 0.11 ppm among the residents and about

0.3 ppm among the daycare workers. In both groups, significant ($p<0.001$) decreases in visual contrast sensitivity were observed when compared with the unexposed referent groups. Storm et al. (2011) recruited adults and children living in New York City buildings with or without colocated dry cleaners for a larger study of visual acuity and contrast sensitivity. The exposed subjects were stratified into low and high exposure (<100 or >100 μg/m^3 tetrachloroethylene) based on 24-hour air samples; exhaled air and blood were also analyzed for tetrachloroethylene. Geometric mean indoor air concentrations of 0.00046, 0.0018, or 0.050 ppm tetrachloroethylene were reported for the referent, low, and high exposure groups of children (n=56, 39, and 11, respectively); for adult participants, the concentrations were 0.00043, 0.0017, or 0.070 ppm (n=49, 43, and 12, respectively). In children, a higher concentration of tetrachloroethylene in indoor air was associated with a higher odds of achieving less than the maximum score (in the poorer performing eye) at a spatial frequency of 12 cycles per degree of visual arc; the effect remained after adjustment for race, ethnicity, and age (adjusted OR 2.64; 95% CI 1.41–5.52). Visual contrast sensitivity of adults was not associated with measures of tetrachloroethylene exposure. A 30-month-old child whose mother worked as a dry cleaner prior to and during pregnancy exhibited decreased contrast sensitivity in the low and intermediate spatial frequency ranges (measured by transient and sweep visual-evoked potentials), when compared with three unexposed 2-year-old children (Till et al. 2003).

Chronic-duration effects on risk of neurological disease: A study of 99 twin pairs (including 49 identical and 50 fraternal pairs) was conducted to evaluate the association between exposure to solvents and Parkinson's disease risk (Goldman et al. 2012). The twin pairs, from the World War II Veteran Twins Cohort, were discordant for Parkinson's disease (one twin had the disease and one did not). The twins completed detailed questionnaires regarding occupational tasks and hobbies, and their exposure to six solvents was estimated from their answers by experts blinded to disease status. Among those ever exposed to tetrachloroethylene, a borderline significant ($p=0.053$) increase in the risk of Parkinson's disease (OR 10.5; 95% CI 0.97–113) was observed. Adjustment for exposure to any other solvent and other potential confounders (head injury, smoking, and zygosity) resulted in minimal change in the OR. Additional studies examining the potential relationship between tetrachloroethylene exposure and Parkinson's disease, especially studies with direct and quantitative measures of exposure, are needed before a conclusion can be drawn.

Perrin et al. (2007) observed a significant increase in the risk for developing schizophrenia among offspring of parents who worked as dry cleaners in Jerusalem. The study group consisted of a population-based cohort of individuals born between 1964 and 1976 (the Jerusalem Perinatal Study). The study collected data on demographics and occupation from birth certificates; these data were then linked to

Israel's national Psychiatric Registry to identify schizophrenia patients. Proportional hazards assessment was used to evaluate the risk of schizophrenia among the 88,829 live offspring followed to 1998. Of 144 offspring of parents employed in dry cleaning, 4 cases of schizophrenia were observed. The relative risk of developing schizophrenia was 3.4 (95% CI 1.3–9.2; p=0.01); this risk was minimally altered when a number of variables, including paternal age, were included in the model. No measure of exposure was included in this analysis. Because information relating schizophrenia risk to tetrachloroethylene exposure is limited to one study with a small number of patients and a surrogate measure of exposure, additional studies are needed to clarify the association, if any, with tetrachloroethylene exposure.

In a case-control study of autism spectrum disorders (ASDs) in California, no association was found between developmental exposure to tetrachloroethylene and diagnosis of ASD in children born in 1994 (Windham et al. 2006). Exposure was estimated using the U.S. EPA annual average Hazardous Air Pollutant (HAP) concentration estimates from 1996. Limitations of this study include use of estimated exposures, lack of addresses during the first trimester of pregnancy, and lack of control for other sources of exposure (e.g., occupational) and confounding variables (e.g., smoking). As with the single studies of Parkinson's disease and schizophrenia, more information is needed to assess the relationship between tetrachloroethylene exposure and autism spectrum disorders.

Neurological Effects in Animals. Neurological effects of tetrachloroethylene exposure in laboratory rodents are qualitatively similar to those seen in human studies. Mice and rats have exhibited anesthetic effects after exposure to high concentrations, while lower concentrations have resulted in effects on visual-evoked potentials, EEG patterns, and neurobehavioral tests of attention, as discussed below.

Neurological signs typical of an anesthetic effect of inhaled tetrachloroethylene have been reported in numerous animal studies of acute exposure durations (see Table 3-1). These clinical signs consist of hyperactivity (excitability), ataxia, hypoactivity, and finally loss of consciousness (Friberg et al. 1953; NTP 1986; Rowe et al. 1952). Rats exposed to 3,000 ppm tetrachloroethylene became anesthetized in several hours, while those exposed to 6,000 ppm were anesthetized in minutes (Rowe et al. 1952). Anesthesia was observed in mice within 2.5 minutes of breathing air containing 6,800 ppm tetrachloroethylene (Friberg et al. 1953). Dogs exposed to 5,000 ppm tetrachloroethylene by face mask for 10 minutes became excited and struggled (Reinhardt et al. 1973); this response may have represented respiratory irritant effects of tetrachloroethylene. Mice inhaling tetrachloroethylene for 4 hours showed signs of anesthesia at a concentration of 2,328 ppm (NTP 1986). Rats became ataxic following exposure to 2,300 ppm for 4 hours (Goldberg et al. 1964). Dyspnea, hypoactivity, hyperactivity, anesthesia, and

ataxia were noted in mice and rats exposed to 1,750 ppm on 6 hours/day, 5 days/week for 2 weeks; these effects were not seen at lower concentrations (up to 875 ppm) (NTP 1986).

Acute exposures also demonstrated effects of tetrachloroethylene on visual and/or somatosensory-evoked potentials, as well as EEG changes, in rats. Male Long-Evans rats exposed for 1.5 hours to concentrations of 250, 500, or 1,000 ppm exhibited reduced amplitude of visual-evoked potentials at all exposure concentrations (Boyes et al. 2009). Albee et al. (1991) reported electrophysiological changes including altered shape, reduced amplitude, and decreased latency of flash-evoked potentials; decreased latency of somatosensory-evoked potentials; and EEG changes in male rats exposed to tetrachloroethylene at 800 ppm 4 hours/day for 4 days. Similar findings were observed when male F344 rats were exposed 6 hours/day for 4 days to 800 ppm tetrachloroethylene as a pilot study in preparation for a subchronic study (Mattsson et al. 1998). Alterations in flash-evoked potentials recorded in the visual cortex were observed at 800 ppm, but not at lower exposure concentrations; cerebellar flash-evoked potentials were not affected by treatment. No treatment-related changes in auditory brainstem responses to clicks and tone pips, somatosensory-evoked potentials, or caudal nerve action potentials were observed, and grip strength was not affected by exposure (Mattsson et al. 1998).

Behavioral alteration has been observed in rodents after acute inhalation exposure to tetrachloroethylene. Impairment of sustained attention was observed in male Long-Evans rats exposed for one hour to concentrations of ≥500 ppm tetrachloroethylene (Oshiro et al. 2008). The degree of impairment increased with duration of exposure (tests of sustained attention were administered at 12-minute intervals during exposure. Open-field behavior (ambulation) was elevated in groups of 10 male rats exposed to 200 ppm tetrachloroethylene of unspecified purity for 6 hours/day for 4 days (Savolainen et al. 1977). Ambulation was significantly increased 1 hour, but not 17 hours, after the last exposure. Biochemical changes in the brains following several additional exposures were reduced ribonucleic acid (RNA) content and increased nonspecific cholinesterase content. There was no histologic examination of brain tissue, so these findings could not be correlated with brain structural damage.

Intermediate-Duration Neurological Effects in Animals. A 13-week study in which rats were exposed to 50, 200, or 800 ppm tetrachloroethylene (6 hours/day, 5 days/week) reported no effect on gait, posture, muscle tone, sensory response, or hind and forelimb grip performance (Mattsson et al. 1992, 1998). At 800 ppm, minimal changes were noted in flash-evoked potentials measured 1 week after the last exposure. The investigators considered the effect nonadverse and indicated that changes in flash-evoked potential can occur in rats exposed to enriched environment (paired housing, access to an exercise wheel,

and handling twice a day by study personnel). Histological changes were not observed in the optic tract, brain, spinal cord, or peripheral nerves. According to the investigators, this study indicates that intermediate-duration exposure of rats to tetrachloroethylene at 800 ppm does not cause serious permanent damage and suggests that if minor acute changes in flash-evoked potentials are prevented, more serious neurological effects will not occur. However, it is not possible to draw a conclusion on the reversibility of the effects without data on the post-exposure time course of these effects.

A multigeneration study in rats suggests that animals may adapt to some of the neurological effects of tetrachloroethylene. Exposure at 1,000 ppm, 6 hours/day, 5 days/week for 11–19 weeks resulted in decreased activity, reduced response to sound, salivation, breathing irregularities, and piloerection (Tinston 1995). The effects were observed only during the first 2 weeks in each generation, and recovery from these effects was noted about 30 minutes before the end of each exposure.

Biochemical changes were reported in brains of rats and Mongolian gerbils exposed by inhalation to tetrachloroethylene. Gerbils exposed to 320 ppm continuously for 3 months followed by a 4-month exposure-free period had changes in levels of S-100 protein, a marker for astrocytes as well as other cells in the peripheral nervous system and skin (Rosengren et al. 1986). Rats exposed to 320 ppm continuously for 30 days had changes in brain cholesterol, lipids, and polyunsaturated fatty acids (Kyrklund et al. 1988). Changes in the fatty acid composition of the brain were also observed in rats continuously exposed to tetrachloroethylene at 320 ppm for 90 days (Kyrklund et al. 1990). Gerbils exposed to 60 or 320 ppm had decreased deoxyribonucleic acid (DNA) content in portions of the cerebrum (Karlsson et al. 1987; Rosengren et al. 1986). Gerbils exposed to 120 ppm continuously for 12 months had altered phospholipid content (phosphatidylethanolamine) in the cerebral cortex and hippocampus (Kyrklund et al. 1984). In another study, gerbils with a similar exposure regimen had decreased taurine content and increased glutamine content in areas of subcortical brain tissue (Briving et al. 1986). These studies are limited by failure to examine nervous tissue histologically in order to correlate biochemical changes with behavioral alterations or with morphologic evidence of brain damage. In addition, all but the Rosengren et al. (1986) study involved exposure to only one concentration of tetrachloroethylene.

In a study designed to examine tetrachloroethylene effects on different regions and different cell types of the brain, Wang et al. (1993) measured brain weight and neuronal and glial markers in rats exposed continuously at 300 or 600 ppm for 4 or 12 weeks. Brain weight was significantly reduced at 600 ppm following both 4 and 12 weeks of exposure. Measurement of neuron-specific enolase, a cytosolic neuronal protein in the frontal cerebral cortex, hippocampus, and brainstem did not show any changes.

The cytosolic marker of glial cells, glial S-100, was significantly reduced in all three brain regions following exposure at 600 ppm for 12 weeks, with the greatest reduction observed in the frontal cerebral cortex. Cytoskeletal elements of neuronal cells (neurofilament 68 kD polypeptide) and glial cells (glial fibrillary acid protein) were significantly reduced in the frontal cerebral cortex at 600 ppm. The neuronal marker was reduced at both 4 and 12 weeks, while the glial marker was reduced only at 12 weeks. In the hippocampus and brainstem, only the glial cytoskeleton protein was significantly reduced following 12 weeks of exposure at 600 ppm. The investigators (Wang et al. 1993) concluded that the frontal cerebral cortex is more sensitive to tetrachloroethylene than other regions of the brain, that cytoskeletal elements are more sensitive than cytosolic proteins, and that in addition to neural cells, glial cells are vulnerable to the effects of tetrachloroethylene.

Chronic-Duration Neurological Effects in Animals. Histologic lesions in the central and peripheral nervous systems have not been observed in chronic inhalation studies in rats and mice (JISA 1993; NTP 1986).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

Reproductive Effects in Humans. Some adverse reproductive effects in men and women have been reported to be associated with occupational exposure to tetrachloroethylene in dry cleaning operations. These effects include menstrual disorders, spontaneous abortion, sperm abnormalities, and decreased fertility. However, exposure in many of these studies was characterized only by occupation, tetrachloroethylene levels were not measured, and coexposure to other solvents could not be ruled out in many studies; thus, no definitive conclusions regarding the association between tetrachloroethylene inhalation and reproductive end points can be made based on the human data.

In a cross-sectional study, female dry cleaning workers in the Netherlands reported more menstrual dysregulation, including oligomenorrhea, unusual cycle length, menorrhagia, dysmenorrhea, and premenstrual syndrome, than laundry workers (Zielhuis et al. 1989). Limitations of the study are lack of exposure measurements, use of a self-administered questionnaire to evaluate effects, lack of follow-up, failure to account for various confounding factors such as smoking, alcohol consumption, and medicinal drugs), and a relatively small study population.

No evidence of a consistent effect on pregnancy outcome was observed in a nested case-control study of 214 cases of low birth weight, congenital malformations, perinatal mortality, or spontaneous abortions identified in a cohort of dry cleaning workers in Scandinavia (Olsen et al. 1990). This study was limited by incomplete participation of all dry cleaning facilities, few controls for life-style factors, and limited exposure information. When analyses of subpopulations in Finland (Kyyrönen et al. 1989) and Sweden (Ahlborg et al. 1990) were conducted, higher odds of spontaneous abortion were reported in tetrachloroethylene-exposed women from Finland, but not Sweden. However, a small group of exposed affected workers was included in the Finnish population, and biological monitoring for tetrachloroethylene was conducted after, rather than concurrent with, the first trimester of pregnancy (Kyyrönen et al. 1989). In addition, few pregnancies occurred among exposed women in the Swedish group (Ahlborg 1990). Other small studies reported increased incidences of spontaneous abortions in Italian dry cleaning workers (Bosco et al. 1986) and Finnish laundry workers (Hemminki et al. 1980); however, only the findings from Hemminki et al. (1980) reached statistical significance.

A case-control study of California women occupationally exposed to tetrachloroethylene in dry cleaning operations suggested that women exposed to tetrachloroethylene and/or trichloroethylene early in gestation had increased probability of spontaneous abortion (unadjusted OR 3.4; 95% CI 1.0–2.0; Windham 1991). In this study, exposure was assessed through telephone interviews; in addition, coexposure to other solvents, along with limited control for confounding factors, limit the reliability of these findings. In a larger, retrospective study of current and past laundry (n=2,711) and dry cleaner workers (n=399) in the United Kingdom (Doyle et al. 1997), females who were dry cleaner operators during or 3 months prior to pregnancy had a higher incidence of spontaneous abortion than non-operator dry cleaner workers (increased ~50%), laundry workers (increased ~30%), or unexposed women (workers not employed in these occupations during or just prior to pregnancy; increased ~45%). The increased risk for dry cleaner operators was significantly elevated compared with non-operators or unexposed women (Doyle et al. 1997). In a survey of 56,012 women in Montreal, Canada, no increases in spontaneous abortion rates, stillbirths, birth defects, or low birth weight were observed among laundry and dry cleaner workers; exposure information was limited to occupation and likely included unexposed individuals (McDonald et al. 1986, 1987).

In a study of semen quality among dry cleaners (n=34), the overall percentages of abnormal sperm were similar in the dry cleaners and 48 unexposed laundry workers (Eskenazi et al. 1991b). However, the sperm cells of dry cleaners were significantly more likely to be round and less likely to be narrow. Men

with the highest exposure levels had sperm with less progressive linear movement and more lateral movement. No effects on sperm counts were noted. A study of the reproductive outcome of 17 of the dry cleaners and 32 of the laundry workers showed that there is some evidence that it may take slightly longer for the wives of dry cleaners to become pregnant and that they seek help for infertility problems more often (Eskenazi et al. 1991a). Spontaneous abortions were not increased in wives of dry cleaners (Eskenazi et al. 1991a). In 20 women occupationally exposed to unspecified concentrations of tetrachloroethylene, a nonsignificant increase in time-to-pregnancy was observed compared to 92 unexposed controls (Sallmen et al. 1995). Exposure concentrations were not provided in this study.

In a retrospective study, time-to-pregnancy was studied in wives of men biologically monitored for exposure to organic solvents (trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, and toluene) by the Finnish Institute of Occupational Health (Sallmén et al. 1998). Exclusion criteria included contraceptive failure in the study pregnancy, infertility treatments, known reproductive health problems, and diabetes. Multivariate analysis study of 282 couples suggested that paternal exposure to organic solvents may be associated with decreased fecundability, after adjustment for age, age at menarche, menstrual cycle variability, frequency of intercourse, maternal and paternal smoking, maternal exposure to organic solvents, and year of pregnancy. Specific data on tetrachloroethylene exposure were available for 17 of the exposed men. Multivariate analysis of this subgroup also suggested a decrease in fecundability with paternal exposure specifically to tetrachloroethylene (adjusted fecundability density ratio: "low" exposure, 0.86 (95% CI 0.40–1.84); and "high" exposure, 0.68 (95% CI 0.30–1.53). Quantitative exposure concentrations were not reported in this study. Other limitations include methodological problems (retrospective, self-administered questionnaire) and use of surrogate exposure data if exposure was not measured at the time the attempt at pregnancy began (data for individual at different time-point or data for another individual in same job at that time-point). An earlier case-referent study conducted by the Finnish Institute of Occupational Health reported no increase in the number of spontaneous abortions in wives of men occupationally exposed to tetrachloroethylene (Taskinen et al. 1989). This study has similar limitations to the more recent study, as well as small subject numbers (4 cases, 17 referents).

Reproductive Effects in Animals. Evidence from a limited number of well-conducted reproductive studies in laboratory animals suggests that tetrachloroethylene is a potential female reproductive toxicant, resulting in decreased number of liveborn pups, increased pre- and postimplantation loss, and increased resorptions. While several additional studies report a lack of reproductive findings, the majority of these have major study limitations (e.g., single-dose exposures, nonstandard protocols, exposure only during

gestation). There is also limited evidence that tetrachloroethylene can damage both male and female gametes.

Effects on gametes have been reported in both male and female laboratory animals in acute- and intermediate-duration studies. Decreased oocyte quality was reported in female Sprague-Dawley rats exposed to 1,700 ppm for 2 weeks, as evidenced by significantly decreased *in vitro* fertilizability of oocytes and reduced number of penetrated sperm per oocyte (Berger and Horner 2003). In this study, exposure to tetrachloroethylene did not affect the serum progesterone levels of female rats. Spermhead abnormalities were significantly increased in CD-1 male mice 4 and 10 weeks after a 5-day exposure to 500 ppm tetrachloroethylene (NOAEL: 100 ppm) (NIOSH 1980). Abnormalities were not observed 1 week after exposure, indicating that spermatocytes and spermatogonia, rather than sperm and/or spermatids, are sensitive to tetrachloroethylene exposure in mice. However, male albino [CRL:COBS CD (SD) BR] rats exposed at 100 or 500 ppm did not demonstrate treatment-related increases in spermhead abnormalities (NIOSH 1980).

Szakmáry et al. (1997) reported adverse reproductive effects in rats and rabbits, but not mice, following exposure during gestation. CFY rats were exposed to 0, 1,500, 4,500, or 8,500 mg/m^3 (0, 221, 664, or 1,254 ppm) tetrachloroethylene on gestation days 1–20. Maternal weight gain was reduced in dams exposed to 664 or 1,254 ppm tetrachloroethylene (37–40% lower than controls). Preimplantation losses were increased (more than double the control percentage) at these exposure levels, but there were no treatment-related increases in postimplantation losses or number of resorptions. Rabbits exposed to 4,500 mg/m^3 (1,254 ppm) tetrachloroethylene on gestation days 7–20 also demonstrated a 58% reduction in maternal body weight gain. Litters were aborted in two treated and one control doe; in addition, four treated does exhibited total fetal resorptions. Postimplantation losses were higher in treated does (31% versus 11% in controls). However, mice exposed to 1,500 mg/m^3 (664 ppm) tetrachloroethylene on gestation days 7–15 did not demonstrate any changes in maternal body weight gain or number of post-implantation losses or resorptions. Additionally, several gestational studies in rats and rabbits, with and without pre-mating exposure, demonstrated no treatment-related effects on reproductive parameters (e.g., fertility index, number of live litters, pre-/postimplantation loss, number of resorptions) at concentrations ranging from 100 to 1,000 ppm (Carney et al.2006; NIOSH 1980; Tepe et al. 1980).

In a multi-generation study, groups of rats were exposed to tetrachloroethylene at 0, 100, 300, or 1,000 ppm for 6 hours/day, 5 days/week for 11 weeks before mating (Tinston 1995). After mating, the males were exposed at all concentrations daily until termination, and the females were exposed at all

concentrations daily until gestation day 20 when they were removed from exposure. One litter was produced in the first generation, and the dams and litters were exposed to all concentrations daily from day 6 to day 29 postpartum. The F1 generation parents were exposed to tetrachloroethylene at 0, 100, 300, or 1,000 ppm for at least 11 weeks before mating. Three litters were produced in the second generation. Dams and F2A litters of the control and 100 ppm exposure groups were exposed daily from day 6 to day 29 postpartum, and dams and F2A litters of the 300 ppm exposure group were exposed daily from day 7 to day 29 postpartum. Dams and F2A litters of the 1,000 ppm group were not exposed during lactation. For all exposure concentrations, dams and F2B litters were not exposed during lactation. The F2C litters were produced by mating unexposed females with male controls and the males exposed to 1,000 ppm.

Exposure at 1,000 ppm resulted in sedation of dams and pups (Tinston 1995). Decreased body weight gain in the parental animals was noted at 1,000 ppm during the pre-mating and lactation periods, but was generally <10%. The proportion of pups born live at 1,000 ppm was significantly lower in the F1A, F2A, and F2B litters (first litter [A] of the F1 generation and first two litters [A and B] of the F2 generation). The incidence of pup mortality during lactation was also significantly increased at 1,000 ppm in the F1A, F2A, and F2B litters. The effects on survival were observed with and without pup exposure suggesting an *in utero* effect rather than a direct effect of tetrachloroethylene. Relative to controls, growth of offspring was reduced during lactation, with the reduction most marked at 1,000 ppm. At the beginning of the pre-mating period for the F1 parents, body weights of males and females were 26 and 24% lower than controls, respectively. After adjustment for initial body weights, growth of females was similar to controls, although growth of the 1,000 ppm males was less than controls. Body weights of offspring in the 100 and 300 ppm groups were generally within 10% of control values. In the F2C litters, there were no statistically significant changes in the proportion of pups born live, pup survival, or growth suggesting that the effects were not male mediated. No effects on reproductive outcome were noted at 300 ppm. The investigators describe treatment-related chronic progressive glomerulonephropathy in the kidneys of adult rats at 1,000 ppm (Tinston 1995). The report indicates that other organs were removed for histological examination, but it is not clear if they were examined, and if they were examined, details of the results are not provided. The 1,000 ppm concentration is considered a serious LOAEL for reproductive effects resulting in a decrease in the number of liveborn pups, and the 300 ppm concentration is considered a NOAEL in rats.

Adverse effects on reproductive performance were not detected in rats exposed by inhalation to 70, 230, or 470 ppm tetrachloroethylene for 28 weeks, as judged by the number of pregnancies, number of litters

conceived, and number of offspring per litter (Carpenter 1937). This older study has numerous limitations including intercurrent disease, nonstandard protocols, rats of undefined strain, and inadequate controls.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

Limited data are available on developmental effects of tetrachloroethylene in humans exposed via inhalation. Evidence from multiple studies in laboratory animals indicates that gestational exposure to tetrachloroethylene affects growth and development, but it is not overtly teratogenic. In animals, developmental effects reported at concentrations as low as 300 ppm included growth retardation and skeletal and soft tissue anomalies, often at maternal exposure concentrations that elicited toxicity. Two available neurobehavior studies of rats exposed during gestation gave conflicting findings; it is not clear whether strain differences may have contributed to the different results.

Forand et al. (2012) conducted a birth outcome analysis in the Endicott, New York area where residents may have been exposed to VOCs via soil vapor intrusion (migration of contamination through the soil into structures through cracks in building foundations). Two exposure areas were identified based on environmental sampling data: one area was primarily contaminated with trichloroethylene (n=1,090 live births) and the other with tetrachloroethylene (n=350 live births). Maternal residence in the tetrachloroethylene-contaminated area was associated with a nonsignificant elevation in the relative risk for cardiac defects, compared with state-wide incidence (excluding New York City). The incidences of low-birth weight, preterm birth, fetal growth restriction, and other birth defects were not elevated in this area. Limitations of the study include the small number of births in the study area, lack of control for potential occupational exposure to tetrachloroethylene, lower socioeconomic status in the study area than the general comparison population, and concurrent exposure to other VOCs. None of the animal studies observed an association between tetrachloroethylene exposure and cardiac defects, as suggested by the human epidemiological study (Forand et al. 2012).

Szakmáry et al. (1997) reported developmental effects in rats, mice, and rabbits exposed to tetrachloroethylene during gestation. Pregnant CFY rats were exposed to 0, 1,500, 4,500, or 8,500 mg/m^3 (0, 221, 664, or 1,254 ppm) tetrachloroethylene on gestation days 1–20. Fetal effects were observed at

the two highest concentrations, and included increased percentages of fetuses per litter with weight retardation, "skeletal retardation," and total malformations. Apart from noting an increased number of offspring with supernumerary ribs, the study authors did not detail the fetal findings. Pregnant C57BL mice were exposed to 0 or 1,500 mg/m^3 (664 ppm) tetrachloroethylene on gestation days 7–15. No effects on litter size, numbers of dead or resorbed fetuses, fetal or placental weights, or percentages of fetuses with growth retardation, "skeletal retardation", or skeletal malformations were noted. An increased percentage of fetuses per litter with internal organ malformations (14% versus 0.8% in controls) was observed, but the nature of the malformations was not reported. Pregnant New Zealand rabbits were exposed to 0 or 4,500 mg/m^3 (1,254 ppm) tetrachloroethylene on gestation days 7–20 of gestation. Postimplantation losses were higher in treated does (31% versus 11% in controls) and 4/16 treated does exhibited total fetal resorptions. No effects on fetal weight, skeletal development, or malformation rates were noted. Fetal effects in rats and rabbits occurred at the same concentrations causing significant reductions (37–58%) in maternal body weight gain. Maternal weight gain was not affected in exposed mice.

A slight but significant increase in maternal and fetal toxicity occurred in Sprague-Dawley rats and Swiss Webster mice exposed to 300 ppm tetrachloroethylene by inhalation on days 6–15 of gestation (Schwetz et al. 1975). However, neither maternal nor fetal toxicity was reported for rats exposed on gestation days 1–18 or 6–18 or in rabbits exposed on gestation days 1–21 or 7–21 by inhalation to 500 ppm tetrachloroethylene, with or without pre-gestational exposure (Hardin et al. 1981; NIOSH 1980). Limitations of this study include use of only one dose level, use of summary and nonquantitative data, and conduct of portions of the study at two separate laboratory facilities. In a more rigorous study, Carney et al. (2006) observed significantly decreased fetal weights in offspring of CD rats exposed to concentrations of 250 or 600 ppm tetrachloroethylene for 6 hours/day on gestation days 6–19. The decrease in body weight was statistically significant when male and female pups were combined (4% less than controls) and for each sex considered separately at 600 ppm (~10% less than controls). Decreased maternal body weight gain was also observed in the dams (Carney et al. 2006). In addition, a nonsignificant increase in the incidence of incomplete ossification of the thoracic vertebral centra (11/21 litters versus 4/10 control litters) was noted at 600 ppm.

In a combined teratogenic and neurodevelopmental study, groups of 30 female Long-Evans rats were exposed to tetrachloroethylene at 0 or 1,000 ppm 2 weeks prior to mating through gestational day 20, prior to mating through confirmation of pregnancy only, or gestation days 1–20. Half of the dams were sacrificed at gestation day 21 for teratological examination (Tepe et al. 1980). The remaining dams were

allowed to deliver, and pups were evaluated for growth and development for up to 18 months (Manson et al. 1981). No developmental or teratogenic effects were observed in the group exposed only prior to gestation. Fetal weight was decreased by 13.5% in both groups with gestational exposure, with no apparent increase in severity due to pre-gestational exposure. Fetuses from dams exposed both before and during gestation, but not gestation-only, exhibited a significant increase in the number of skeletal anomalies (e.g., delayed sternal ossification and missing vertebra). Both groups exposed during gestation demonstrated an increase in the incidence of kidney dysplasia, but there was only a significant increase in total soft tissue anomalies among fetuses exposed during gestation only. No overt maternal toxicity was observed during any of the exposure paradigms. None of the offspring exhibited alterations in survival, growth, neurobehavior, or gross pathologies, regardless of treatment paradigm.

In contrast, neurobehavioral and neurochemical alterations were reported in offspring of Sprague-Dawley rats exposed to 900 ppm tetrachloroethylene on gestation days 7–13 or 14–20 (NOAEL 100 ppm) (Nelson et al. 1980). Dams had reduced feed consumption and weight gain, without liver or kidney histological alterations. Pups of dams exposed to 900 ppm on gestation days 7–13 had decreased performance during tests of neuromuscular ability (ascent on a wire mesh screen and rotarod balancing) on certain days. Offspring (before weaning) from dams exposed to 900 ppm on days 14–20 performed poorly on the ascent test on test day 14 only, but later in development, their performance in the rotarod balancing test was superior to the controls, and they were more active in an open-field test. Brains of 21-day-old offspring exposed to 900 ppm prenatally had significant decreases in neurotransmitters (dopamine in those exposed on gestation days 14–20 and acetylcholine in those exposed on days 7–13 or 14–20). There were no microscopic brain lesions. Changes in brain fatty acid composition were observed in the offspring of guinea pigs exposed to tetrachloroethylene at 160 ppm during gestation days 33–65 (Kyrklund and Haglid 1991). Measurements of brain lipids did not show any effects. The investigators concluded that changes in fatty acid composition in the brains of developing animals were not greater than in adult animals exposed to tetrachloroethylene.

The highest NOAEL values and all reliable LOAEL values for developmental effects each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

In humans, tetrachloroethylene exposure may be associated with increased risk of cancer. As discussed further below, the highest quality epidemiological studies suggest associations between tetrachloro-

ethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma. Other epidemiology studies suggest possible associations with other cancer sites (esophageal, kidney, lung, liver, cervical, and breast cancer), but the data are more limited and/or inconsistent. Studies in animals (JISA 1993; NTP 1986) demonstrate increased risks of liver tumors and mononuclear cell leukemias after chronic exposure to tetrachloroethylene.

Numerous observational, retrospective cohort, and case-control cancer studies have assessed possible associations between exposure to tetrachloroethylene and cancer. The EPA (2012a) summarized a large number of epidemiological studies and selected those studies considered to have been of adequate quality and with a high probability of tetrachloroethylene exposure among individual subjects, and used these to assess possible associations between exposure to tetrachloroethylene and selected cancers. The EPA Integrated Risk Information System (IRIS) Toxicological Review for Tetrachloroethylene (EPA 2012a) may be consulted for a detailed discussion of available epidemiological data for tetrachloroethylene.

Upon critical review of the available epidemiological data regarding the possible carcinogenicity of tetrachloroethylene, the National Research Council (NRC 2010) concluded that there was suggestive evidence for an association between tetrachloroethylene exposure and lymphoma, despite weak and sometimes inconsistent data. NRC (2010) concluded that there was limited evidence from epidemiological studies for an association with esophageal cancer, and insufficient evidence for an association with other cancer types including liver, kidney, cervical, lung, and bladder cancer. After the NRC (2010) review, EPA (2012a) considered 27 additional epidemiological studies; these studies, with the data also reviewed by NRC (2010), formed the basis for the EPA (2012a) conclusion that the epidemiological data supported a pattern of association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma.

EPA (2012a) relied upon three cohort studies (Blair et al. 2003; Calvert et al. 2011; Lynge et al. 2006) and one large case-control study (Pesch et al. 2000), all judged to provide relatively high-quality exposure assessments, as the basis for the association between tetrachloroethylene exposure and bladder cancer. Calvert et al. (2011) reported an increased standardized mortality ratio (SMR) for bladder and other urinary cancers (SMR 2.59; 95% CI 1.24–4.76) among U.S. dry cleaners exposed to tetrachloroethylene along with other dry cleaning solvents. In addition, Lynge et al. (2006) observed a significant increase in the relative risk of bladder cancer among Nordic dry cleaners (rate ratio 1.44; 95% CI 1.07–1.93). Pesch et al. (2000) reported a significantly increased OR for urothelial cancer among men in the highest exposure group ("substantial" exposure) when exposure was assessed by job-task exposure matrix (OR

1.8; 95% CI 1.1–3.1); the ORs also increased over the exposure gradient from medium to high and substantial.

EPA (2012a) cited the results of Calvert et al. (2011), Selden and Ahlborg (2011), Radican et al. (2008), Boice et al. (1999), and Anttila et al. (1995), all cohort studies with relatively reliable exposure assessments, in their finding of an association between tetrachloroethylene exposure and non-Hodgkin's lymphoma. Calvert et al. (2011) observed nonsignificant increased standardized mortality ratios (SMRs) of 1.57 (95% CI 0.78–2.81) and 2.46 (95% CI 0.90–5.36) for non-Hodgkin's lymphoma among 1,704 dry cleaning union members and among 618 dry cleaner employees at facilities using only tetrachloroethylene (respectively). Selden and Ahlborg (2011) reported a significantly increased risk for non-Hodgkin's lymphoma among male dry cleaners, but not female dry cleaners, in Sweden; the SIRs were 2.05 (95% CI 1.30–3.07) in men (n=2,810) and 1.07 (95% CI 0.70–1.57) in women (n=6,630). Radican et al. (2008) reported the results of an extended follow-up of 14,455 aircraft maintenance workers. Among those who had ever worked with tetrachloroethylene, the hazard ratios (HRs) for mortality from non-Hodgkin's lymphoma were nonsignificantly elevated (HR 2.32; 95% CI 0.75–7.15 among men; HR 2.35; 95% CI 0.52–10.71 among women) compared with those workers with no chemical exposure (Radican et al. 2008). Similarly, Boice et al. (1999) observed an increased SMR for non-Hodgkin's lymphoma in aerospace workers with routine exposure to tetrachloroethylene (SMR 1.70; 95% CI 0.73–3.34; n=2,631 exposed workers). Analysis of the cohort by years of exposure and using an unexposed internal referent group did not show a significant trend ($p>0.2$) for increased risk with years of exposure (Boice et al. 1999). In a follow-up on this cohort, Lipworth et al. (2011, a study not considered by EPA [2012a]) reported a SMR of 1.43 (95% CI 1.0–1.98) for non-Hodgkin's lymphoma among 5,830 workers exposed to tetrachloroethylene. Anttila et al. (1995) observed a nonsignificantly increased SIR for non-Hodgkin's lymphoma among Finnish workers with tetrachloroethylene exposure (SIR 3.76; 95% CI 0.77–11.0; n=849 workers). While some of these studies did not observe statistically significant increases in risk of non-Hodgkin's lymphoma, they demonstrate a consistent pattern of increased risk across a large number of subjects.

The studies used by EPA (2012a) as the primary basis for finding an association with multiple myeloma were Radican et al. (2008) and a case-control study by Gold et al. (2010a, 2010b). Radican et al. (2008) reported a significantly increased HR for multiple myeloma among female aircraft workers exposed to tetrachloroethylene (HR 7.84; 95% CI 1.43–43.06). Gold et al. (2010a, 2010b) reported increases in ORs with estimates of cumulative exposure to tetrachloroethylene; with the longest exposure duration, the OR was 2.5 (95% CI 1.1–5.4); a similar result was obtained when latency to tumor formation was considered.

Overall, the evidence for an association between human exposure to tetrachloroethylene and cancers is limited, but suggests that cancers of the bladder and lymphoreticular system may be increased in exposed persons. A large number of other epidemiological studies is available, and among these are studies that suggest a possible association with esophageal, kidney, lung, liver, cervical, and breast cancer. The epidemiological data for these other tumor sites is much weaker, with more inconsistent findings, a lack of exposure-response data, and/or important confounding factors that are not adequately considered (EPA 2012a).

Evidence for an association between exposure to tetrachloroethylene and increased risk of developing cancer is provided by animal experiments. Available cancer bioassays report increased incidence and severity of mononuclear cell leukemia in male and female rats, as well as reduced time to death from mononuclear cell leukemia in female rats, after inhalation exposure (JISA 1993; NTP 1986); in addition, both inhalation and oral exposures of mice have resulted in increased incidences of hepatic tumors in both sexes (NCI 1977; NTP 1986).

A 103-week inhalation toxicity/carcinogenicity study of tetrachloroethylene was conducted using male and female F344 rats and B6C3F1 mice. Exposure levels were 0, 200, or 400 ppm tetrachloroethylene for rats and 0, 100, or 200 ppm tetrachloroethylene for mice (NTP 1986). In rats, there were significant and dose-related increases in the incidences of mononuclear cell leukemia in exposed males and females (males: 28/50, 37/50, and 37/50 in control, 200 ppm, and 400 ppm groups, respectively; females: 18/50, 30/50, and 29/50 in control, 200 ppm, and 400 ppm groups, respectively). This neoplasm occurs spontaneously in F344 rats, and incidences of mononuclear cell leukemia in control groups (56% for males, 36% for females) for this study were higher than for historical chamber controls for the laboratory or for untreated controls from the NTP database. However, NTP's Board of Scientific Counselors considered the incidence of rat leukemias to be a valid finding despite high background frequencies because there was a decreased time to the onset of the disease and the disease was more severe in treated animals than in control animals.

Low incidences of renal tubular cell adenomas or adenocarcinomas (1/49, 3/49, and 4/50 in control, 200 ppm, and 400 ppm groups, respectively) occurred in male rats (NTP 1986). Although the incidence of these tumors was not statistically significant, the fact that there was any increase was itself significant because these tumors are considered uncommon in untreated male rats. In mice of both sexes exposed to 100 or 200 ppm, there were significantly increased incidences of hepatocellular neoplasms (Table 3-2).

Table 3-2. Hepatocellular Neoplasms in Mice Exposed to Tetrachloroethylene for 103 Weeks by Inhalation[a]

Study and tumor type	Control		100 ppm		200 ppm	
NTP 1986 (B6C3F1 mice)	Male	Female	Male	Female	Male	Female
Hepatocellular adenoma	12/49 (24%)	3/48 (16%)	8/49 (12%)	6/50 (12%)	19/50 (38%)	2/50 (4%)
Hepatocellular carcinoma	7/49 (14 %)	1/48 (2%)	25/49 (51%)	13/50 (26%)	26/50 (58%)	36/50 (72%)
Hepatocellular adenoma or carcinoma	17/49 (35%)	4/48 (8%)	31/49 (63%)	17/50 (34%)	41/50 (82%)	38/50 (76%)

	Control		10 ppm		50 ppm		250 ppm	
JISA 1993 (Crj:BDF1 mice)	Male	Female	Male	Female	Male	Female	Male	Female
Hepatocellular adenoma	7/50 (14%)	3/50 (6%)	13/50 (26%)	3/47(6%)	8/50 (16%)	7/49 (14%)	26/50 (52%)	16/49 (33%)
Hepatocellular carcinoma	7/50 (14%)	0/50	8/50 (16%)	0/47	12/50 (20%)	0/49	25/50 (50%)	14/49 (29%)
Hepatocellular adenoma or carcinoma	13/50 (26%)	3/50 (6%)	21/50 (42%)	3/47(6%)	19/50 (38%)	7/49 (14%)	40/50 (80%)	33/49 (67%)

[a]Data are presented as the number of neoplasms found per total number of animals in each exposure group. Percentages are given in parentheses.

Sources: NTP 1986; JISA 1993

Study limitations include several instances of rats and mice loose from their cages within the exposure chambers, with the potential for small aberrations in exposure, as well as elevated incidences of mononuclear cell leukemia in control rats, and liver tumors in mice.

A similar 104-week inhalation toxicity/carcinogenicity study of tetrachloroethylene was conducted using male and female F344DuCrj rats and Crj:BDF1 mice (JISA 1993). Exposure levels were 0, 50, 200, or 600 ppm tetrachloroethylene for rats and 0, 10, 50, or 250 ppm tetrachloroethylene for mice. In rats, there was a dose-related trend in the incidence of monocytic leukemia of the spleen (males: 11/50, 14/50, 22/50, 27/50; females: 10/50, 17/50, 16/20, 19/50). This increase was statistically significant only in male rats exposed to 600 ppm. In mice, there was a dose-related trend in the incidences of hepatocellular adenoma (males 7/50, 13/50, 8/50, 26/50; females: 3/50, 3/47, 7/49, 16/49) and carcinoma (males: 7/50, 8/50, 12/50, 25/50; females: 0/50, 0/47, 0/49, 14/49). Increased incidences of hepatocellular adenoma and carcinoma were statistically significant in both sexes exposed to 250 ppm (see Table 3-2). Dose-related trends were also noted for incidences of tumors of the Harderian gland and hemangioendotheliomas of the liver and spleen in males, but the incidences were not significantly different from controls at any exposure level.

In summary, the human epidemiological data on cancers in occupationally-exposed groups provide suggestive evidence for an association with bladder cancer, non-Hodgkin's lymphoma, and multiple myeloma (EPA 2012a). Following inhalation exposure to tetrachloroethylene, mononuclear cell leukemia was observed in rats and hepatic tumors were observed in mice (JISA 1993; NTP 1986). Both mononuclear cell leukemia and hepatic tumors are common in rats and mice, respectively, and the mode of action by which tetrachloroethylene induces these neoplasia is not known; thus, the relevance of these tumors to humans is uncertain. Further discussion of the relevance of tumors in animals exposed to tetrachloroethylene to humans is presented in Chapter 2. The cancer effect levels (CELs) for rats and mice are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2 Oral Exposure

3.2.2.1 Death

Oral exposure to large doses of tetrachloroethylene may lead to death from central nervous system depression. While no reliable information in humans is available, rats and mice have died after

intermediate-duration exposures as low as 1,780 and 1,000 mg/kg/day, respectively (NCI 1977; Philip et al. 2007).

One human death has been reported following oral treatment with 3 mL (152 mg/kg) of tetrachloroethylene for hookworm infestation (Chaudhuri and Mukerji 1947). This individual was a severely emaciated "street beggar" with preexistent chronic malnutrition and septic cholecystitis; thus, it is difficult to determine the specific cause of his death and the relevance of this death to healthy humans.

Single-dose LD_{50} values of 3,835 and 3,005 mg/kg were determined for male and female rats given tetrachloroethylene by gavage in 4% Emulphor in water. Death occurred within 24 hours after dosing and was preceded by tremors, ataxia, and central nervous system depression (Hayes et al. 1986). When given in corn oil, half of the female rats treated with a single dose of 5,000 mg tetrachloroethylene/kg died (Berman et al. 1995). Philip et al. (2007) reported an oral LD_{50} of 4,500 mg/kg tetrachloroethylene when administered in 5% Emulphor to male Swiss-Webster mice; deaths occurred between 72 and 96 hours postdosing. An oral LD_{50} of 8,139 mg/kg was reported for mice treated with undiluted tetrachloroethylene (Wenzel and Gibson 1951).

A single death was observed among five female Wistar rats given daily gavage doses of 2,400 mg/kg/day tetrachloroethylene in corn oil in a 32-day study (Jonker et al. 1996). The timing and cause of death were not reported, but the rats in this group exhibited signs of severe central nervous system depression immediately after dosing.

When Osborne-Mendel rats of each sex received tetrachloroethylene in corn oil by gavage at doses of 316, 562, 1,000, 1,780, or 3,160 mg/kg 5 days/week for 6 weeks, deaths (number unspecified) occurred in both males and females at the two highest doses but not at ≤1,000 mg/kg (NCI 1977). Ten percent lethality (2/20) was observed in male Swiss Webster mice given daily gavage doses of 1,000 mg/kg/day tetrachloroethylene in 5% Emulphor for 1 for 30 days; no deaths occurred at the lower doses of 150 or 500 mg/kg/day (Philip et al. 2007). The timing of deaths was not reported, but the fatalities were attributed to central nervous system depression based on observations of tremors and ataxia prior to death.

In a chronic bioassay of tetrachloroethylene administered by gavage to rats and mice, compound-related mortality occurred as a result of toxic nephropathy in both species and hepatocellular tumors in mice (NCI 1977). Increased deaths occurred in groups of male and female rats exposed to 471 and 474 mg/kg/day tetrachloroethylene, respectively, 5 days/week for 78 weeks. Similarly exposed mice had

increased numbers of deaths at doses of 536 and 386 mg/kg/day for males and females, respectively (NCI 1977). This study is discussed in Sections 3.2.2.2 and 3.2.2.7.

All reliable LOAEL and LD_{50} values for death in each species are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2. No studies examining musculoskeletal or ocular effects in humans or animals after oral exposure to tetrachloroethylene were located.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to tetrachloroethylene. In a chronic bioassay, microscopic examination of the lungs did not reveal any effects in rats treated by gavage with tetrachloroethylene at doses up to 941 mg/kg/day or in mice at doses up to 1,072 mg/kg/day, doses that were associated with increased mortality (NCI 1977).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to tetrachloroethylene. However, cardiovascular effects from chronic ingestion of solvent-contaminated (including tetrachloroethylene) drinking water were investigated in family members of patients with leukemia in Woburn, Massachusetts (Byers et al. 1988). Fourteen of 25 adults complained of cardiac symptoms of tachycardia at rest, palpitations, or near syncope. Eleven of these were selected for detailed testing, which included resting and exercise tolerance electrocardiograms, Holter monitoring, echocardiograms, and serum lipid levels. Of these 11 people, 8 had serious ventricular dysfunctions, 7 had multifocal premature ventricular beats, and 6 required cardiac medication. None of the subjects had clinically significant coronary artery disease. No rationale was given as to the factors that were involved in the selection of the 11 given extensive testing. No background information on family history of heart disease, smoking habits, or occupational history was given for any of the 25 family members.

In a chronic bioassay, microscopic examination of the heart did not reveal any effects in rats treated by gavage with tetrachloroethylene at doses up to 941 mg/kg/day or in mice at doses up to 1,072 mg/kg/day, both of which were doses associated with increased mortality (NCI 1977).

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344)	once (GO)				5000 F (50% died)	Berman et al. 1995	
2	Rat (Fischer- 344)	single dose (G)		2500		3200 (increased mortality)	Dow Chemical 1983	
3	Rat (Sprague-Dawley)	once (G)				3835 M (LD50) 3005 F (LD50)	Hayes et al. 1986	
4	Rat (Fischer- 344)	single dose (G)				2500 M (increased mortality)	Wall and Carreon 1984	
5	Mouse (Swiss-Webster)	once (G)				4500 M (LD50)	Philip et al. 2007	
6	Mouse (Swiss-Webster)	once (G)				8139 M (LD50)	Wenzel and Gibson 1951	
Systemic								
7	Rat (Fischer- 344)	14 d (GO)	Hepatic	500 F	1500 F (increased relative liver weights; increased alanine aminotransferase; hepatocellular hypertorphy)		Berman et al. 1995	
			Renal	1500 F				
			Endocr	1500 F				

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
8	Rat (Fischer- 344)	10 d 1x/d (GO)	Hepatic		1000 M (increased liver to body weight ratio)		Goldsworthy and Popp 1987	
			Bd Wt	1000 M				
9	Rat (Wistar)	5d (GO)	Hepatic	500 M	1000 M significatly increased liver weights; induction of CYP2B P450 enzymes; induction of phase II drug-metabolizing enzymes.		Hanioka et al. 1995	
			Bd Wt	1000 M	2000 M (body weights 16% lower than controls)			
10	Rat (Fischer- 344)	Gd 6-19 (GO)	Bd Wt			900 F (about 25% decrease in body weight gain)	Narotsky and Kavlock 1995	
11	Rat (Fischer- 344)	7 d (G)	Bd Wt	1000 M			Potter et al. 1996	
12	Rat (Wistar)	14 d 1x/d (G)	Hepatic		1000 F (increased serum enzymes and histopathology including minimal periportal lymphocytic infiltration, inflammation, and hepatocellular necrosis)		Rajamanikandan et al. 2012	

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
13	Rat (Fischer- 344)	11 d (GO)	Hepatic	1000 M			Schumann et al. 1980	
			Bd Wt	500 M		1000 M (22% decrease in body weight gain)		
14	Mouse (B6C3F1)	10 d 1x/d (G)	Hepatic		1000 M increased liver to body weight ratios; peroxisomal proliferation		Goldsworthy and Popp 1987	
			Renal		1000 M peroxisomal proliferation			
			Bd Wt	1000 M				
15	Mouse (Swiss-Webster)	14 days Daily (G)	Hepatic		150 M (>twofold increase in serum ALT)		Philip et al. 2007	
16	Mouse (B6C3F1)	11 d (GO)	Hepatic		100 M (hepatocellular swelling)		Schumann et al. 1980	
			Bd Wt	1000 M				
Immuno/ Lymphoret								
17	Rat (Fischer- 344)	14 d (GO)		1500 F			Berman et al. 1995	
18	Rat (Wistar)	5d (GO)		1000 M	2000 M (atrophy of the spleen and thymus)		Hanioka et al. 1995	

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
19	Rat (Wistar)	2 wk (W)			0.0009 (increased dermal lymphocyte infiltration and perivascular mast cell accumulation)		Seo et al. 2008a	
20	Mouse (ICR)	2 wk (W)		0.26			Seo et al. 2012	
Neurological								
21	Human	once (C)				116 M (amnesia; dizziness; hallucinations)	Haerer and Udelman 1964	
22	Human	once				108 M (unconsciousness)	Kendrick 1929	
23	Rat (Sprague-Dawley)	once (GO)			50 M (increased seizure threshold)		Chen et al. 2002	
24	Rat (Fischer- 344)	single dose (G)			1300 (lethary, loss of coordination)		Dow Chemical 1983	
25	Rat (Fischer- 344)	once		500 F		1500 F (lacrimation and gait score significantly increased; motor activity significantly decreased)	Moser et al. 1995	

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
26	Rat (Fischer- 344)	Gd 6-19 (GO)				900 F (ataxia that lasted about 4 hours after dosing)	Narotsky and Kavlock 1995	
27	Rat (Fischer- 344)	single dose (G)			1300 M (lethargy and loss of coordination)		Wall and Carreon 1984	
28	Rat (Sprague-Dawley)	Once (GO)		160 M	480 M (suppression of operant response behavior)		Warren et al. 1996	
Reproductive								
29	Rat (Fischer- 344)	Gd 6-19 (GO)				900 F (significant increase in resorptions)	Narotsky and Kavlock 1995	
Developmental								
30	Rat (Fischer- 344)	Gd 6-19 (GO)				900 F (increased postnatal deaths; increased micro/anophthalmia)	Narotsky and Kavlock 1995	
31	Mouse (NMRI)	7 d (GO)			5 M (increased activity at 60 days of age)		Fredriksson et al. 1993	
INTERMEDIATE EXPOSURE								
Death								
32	Rat (Wistar)	32 d Daily (GO)				2400 F (1/5 died)	Jonker et al. 1996	

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
33	Rat (Osborne-Mendel)	6 wk 5d/wk (GO)					1780	(number of deaths not specified)	NCI 1977	
34	Mouse (Swiss-Webster)	30 days Daily (G)					1000 M	(2/20 died)	Philip et al. 2007	
Systemic										
35	Rat (Sprague-Dawley)	90 d (W)	Hemato	1400					Hayes et al. 1986	
			Hepatic	400	1400	increased liver/body weight ratio				
			Renal	14 M	400 M	increased kidney/body weight ratio				
			Bd Wt	14 F	400 F	(18% decrease in body weight gain)	1400 F	(24% decrease in body weight gain)		

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (Wistar)	32 d Daily (GO)	Hepatic	600 F	2400 F (increased relative liver weight; increased alanine aminotransferase and aspartate aminotransferase)		Jonker et al. 1996	
			Renal	600 F	2400 F (urinalysis changes, increased relative kidney weight, multifocal tubular vacuolation and karyomegaly)			
			Bd Wt	2400 F				
37	Rat (Osborne-Mendel)	6 wk 5d/wk (GO)	Bd Wt	1000			NCI 1977	
38	Rat (Osborne-Mendel)	7wk 5d/wk (GO)	Hepatic		995 M (increased liver weight; increased Type II GGT and foci with or without an initiator)		Story et al. 1986	
39	Mouse (Swiss- Cox)	6 wk 5d/wk (GO)	Hepatic	20 M	100 M (increased relative liver weight; increased liver triglycerides)	200 M (hepatic necrosis)	Buben and O'Flaherty 1985	

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
40	Mouse (Swiss-Webster)	15 d Daily (GO)	Hepatic		3000 (increased relative liver weight, altered hepatic glycolytic and gluconeogenic enzyme activities, and liver histopathology)		Ebrahim et al. 1996	
			Renal		3000 (increased relative kidney weight; hypercellular glomeruli)			
			Bd Wt	3000				
41	Mouse (Swiss-Webster)	15 d Daily (GO)	Hemato		3000 M (decr Hb, Hct, RBC and platelet counts; incr WBC count)		Ebrahim et al. 2001	
42	Mouse (B6C3F1)	6 wk 5d/wk (GO)	Bd Wt			562 F (30% decrease in body weight gain)	NCI 1977	
43	Mouse (Swiss-Webster)	30 days Daily (G)	Hepatic	150 M	500 M (centrilobular fatty degeneration and single cell necrosis)		Philip et al. 2007	
			Renal	1000 M				

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
44	Rat (Wistar)	4 wk (W)			0.0009 (increased relative weight of mesenteric lymph nodes; enlargement of lymphoid nodules with clearly visible germinal centers)		Seo et al. 2008a	
45	Mouse (ICR)	4 wk (W)			0.0025 (enhancement of passive cutaneous anaphylaxis reaction)		Seo et al. 2012	
Neurological								
46	Rat (Sprague-Dawley)	8 wk 5 d/wk (GO)			5 M (impaired nociception and increased seizure threshold)		Chen et al. 2002	
47	Rat (Wistar)	32 d Daily (GO)				2400 F (severe but transient signs of CNS depression)	Jonker et al. 1996	
CHRONIC EXPOSURE								
Death								
48	Rat (Osborne-Mendel)	78 wk 5d/wk (GO)				471 M (decreased survival) 474 F (decreased survival)	NCI 1977	
49	Mouse (B6C3F1)	78 wk 5d/wk (GO)				536 M (reduced survival) 386 F (reduced survival)	NCI 1977	

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
50	Rat (Osborne-Mendel)	78 wk 5d/wk (GO)	Resp	941			NCI 1977	
			Cardio	941				
			Gastro	941				
			Hepatic	941				
			Renal			471 M nephropathy		
						474 F nephropathy		
			Endocr	941				
			Dermal	941				
			Bd Wt	941				
51	Mouse (B6C3F1)	78 wk 5d/wk (GO)	Resp	1072			NCI 1977	
			Cardio	1072				
			Gastro	1072				
			Hepatic	1072				
			Renal			536 M nephropathy		
						386 F nephropathy		
			Endocr	1072				
			Dermal	1072				
			Bd Wt	1072				

Table 3-3 Levels of Significant Exposure to Tetrachloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
52	Human	106 mo average			2.3[b]		Cavalleri et al. 1994	POD (2.3 mg/kg/day) derived from PBPK model-based route-to-route extrapolation
Cancer								
53	Mouse (B6C3F1)	78 wk 5d/wk (GO)				536 M CEL: hepatocellular carcinomas	NCI 1977	
						386 F CEL: hepatocellular carcinomas		

a The number corresponds to entries in Figure 3-2.

b Used to derive a chronic-duration oral minimal risk level (MRL) of 0.008 mg/kg/day for tetrachloroethylene; the MRL is based on the equivalent continuous exposure LOAEL of 1.7 ppm from an inhalation study; a PBPK model was employed to determine the equivalent oral dose (2.3 mg/kg/day) using an internal dose metric of 24-hour AUC of the tetrachloroethylene blood concentration-time curve. The route-to-route extrapolated LOAEL of 2.3 mg/kg/day was divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL), and a modifying factor of 3 for database deficiencies (for inadequate information on potential low-dose immune system effects). ATSDR has adopted the chronic-duration oral MRL as the acute-duration and intermediate-duration oral MRLs. See Appendix A for detailed discussion of the oral MRLs for tetrachloroethylene.

ad lib = ad libitum; B = both sexes; Bd Wt = body weight; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Metab = metabolism; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Occup = occupational; Pmd = pre-mating day; Pnd = post-natal day; Ppd = post-parturition day; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Tetrachloroethylene - Oral

Acute (≤14 days)

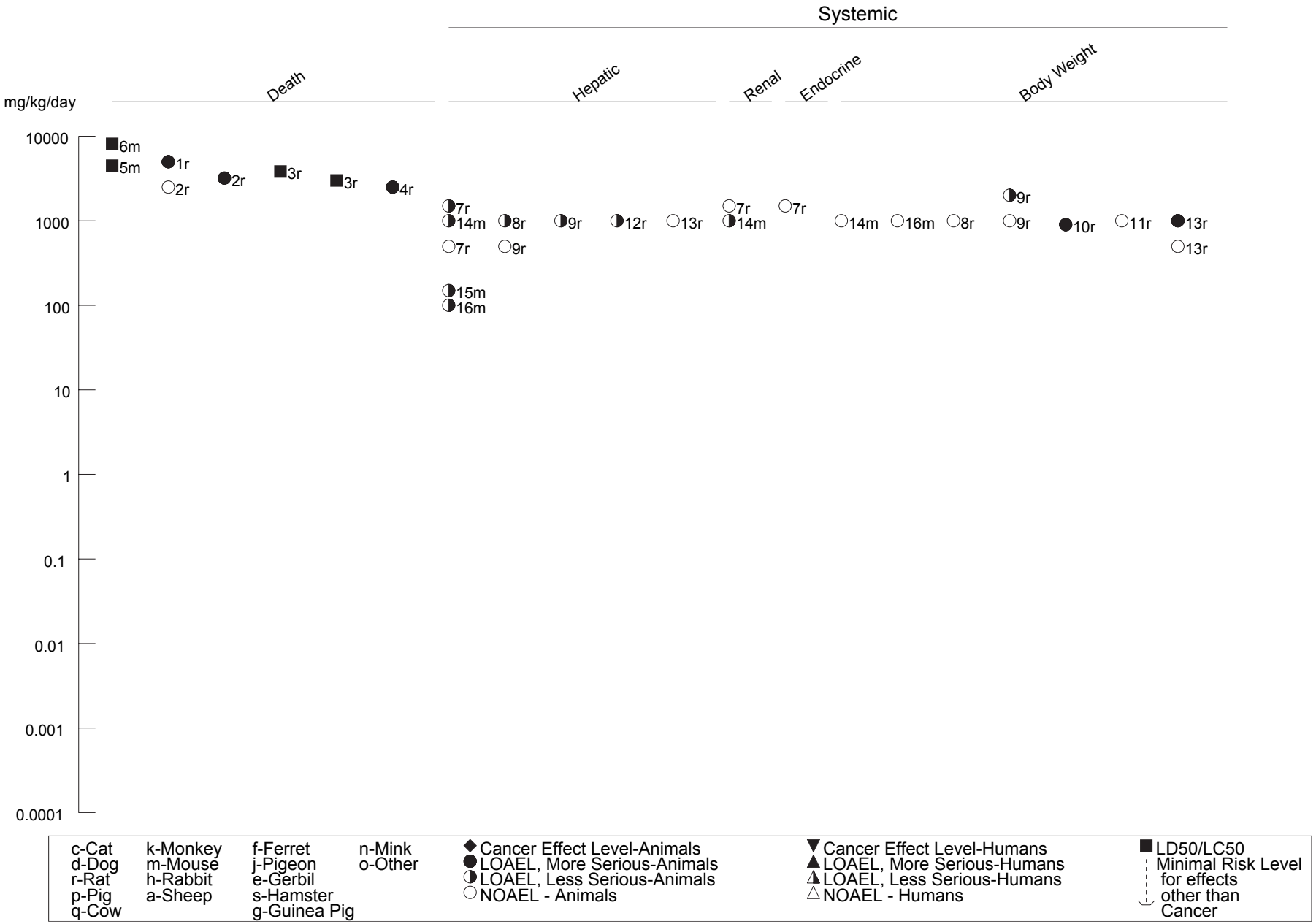


Figure 3-2 Levels of Significant Exposure to Tetrachloroethylene - Oral *(Continued)*

Acute (≤14 days)

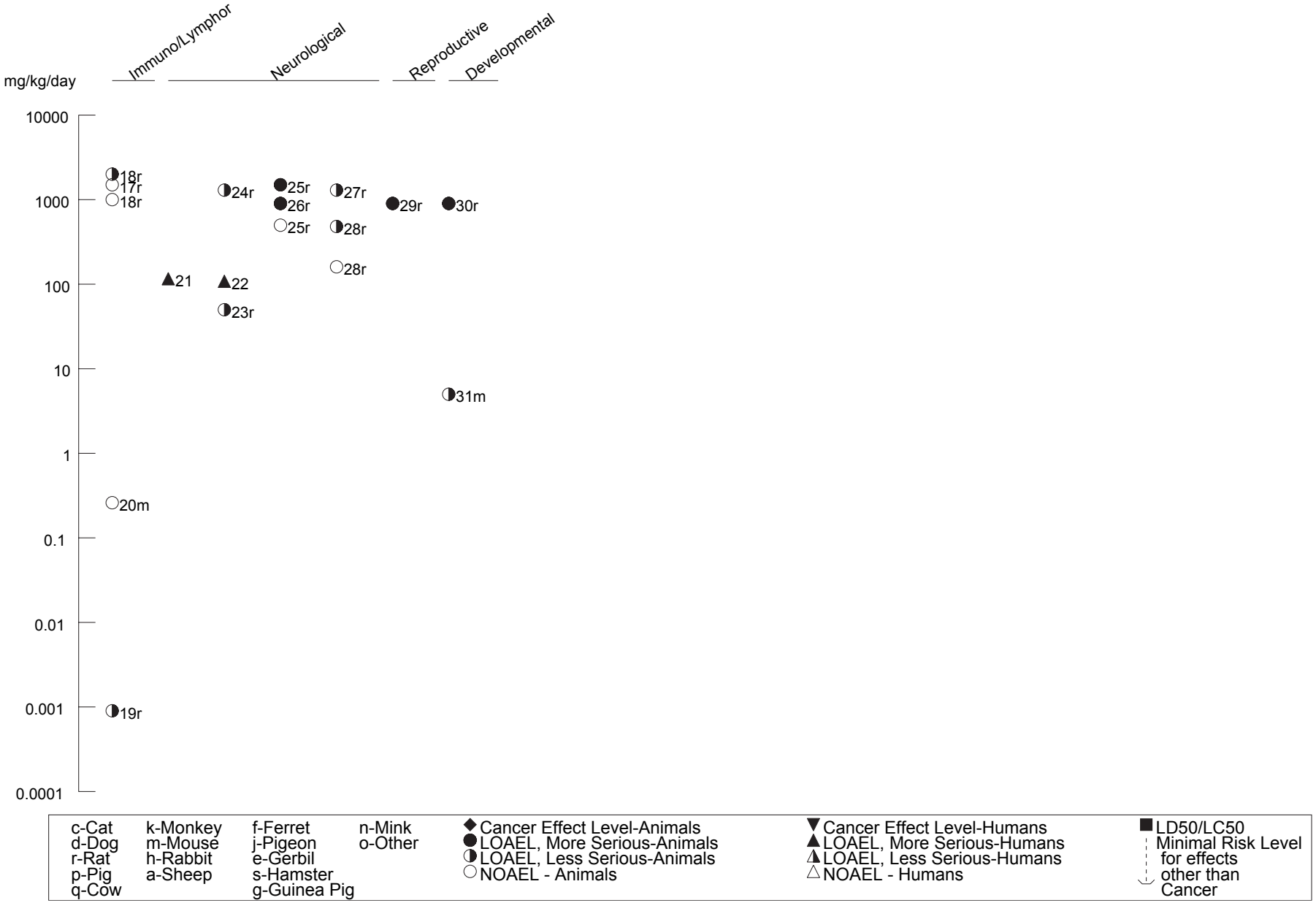


Figure 3-2 Levels of Significant Exposure to Tetrachloroethylene - Oral *(Continued)*

Intermediate (15-364 days)

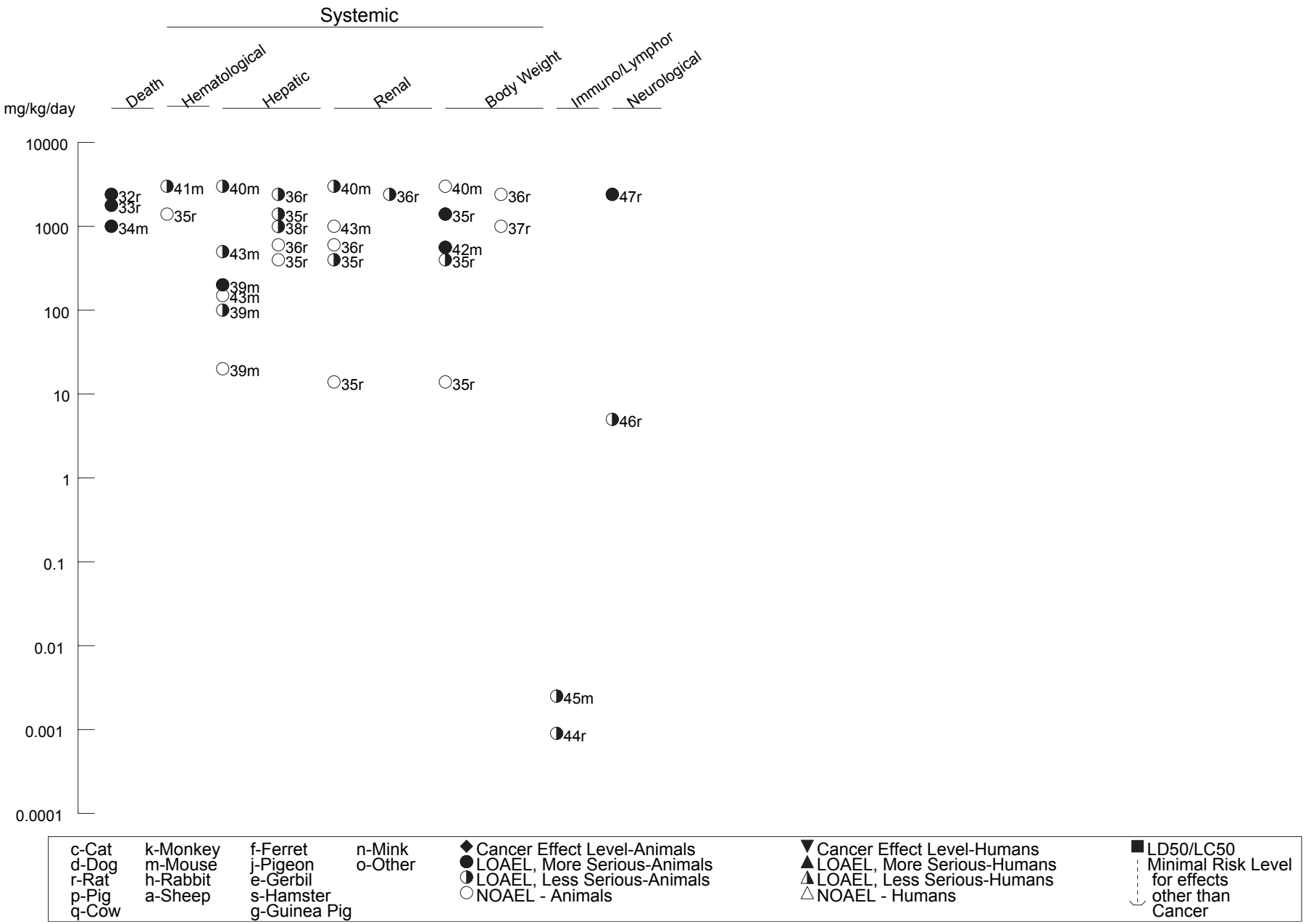
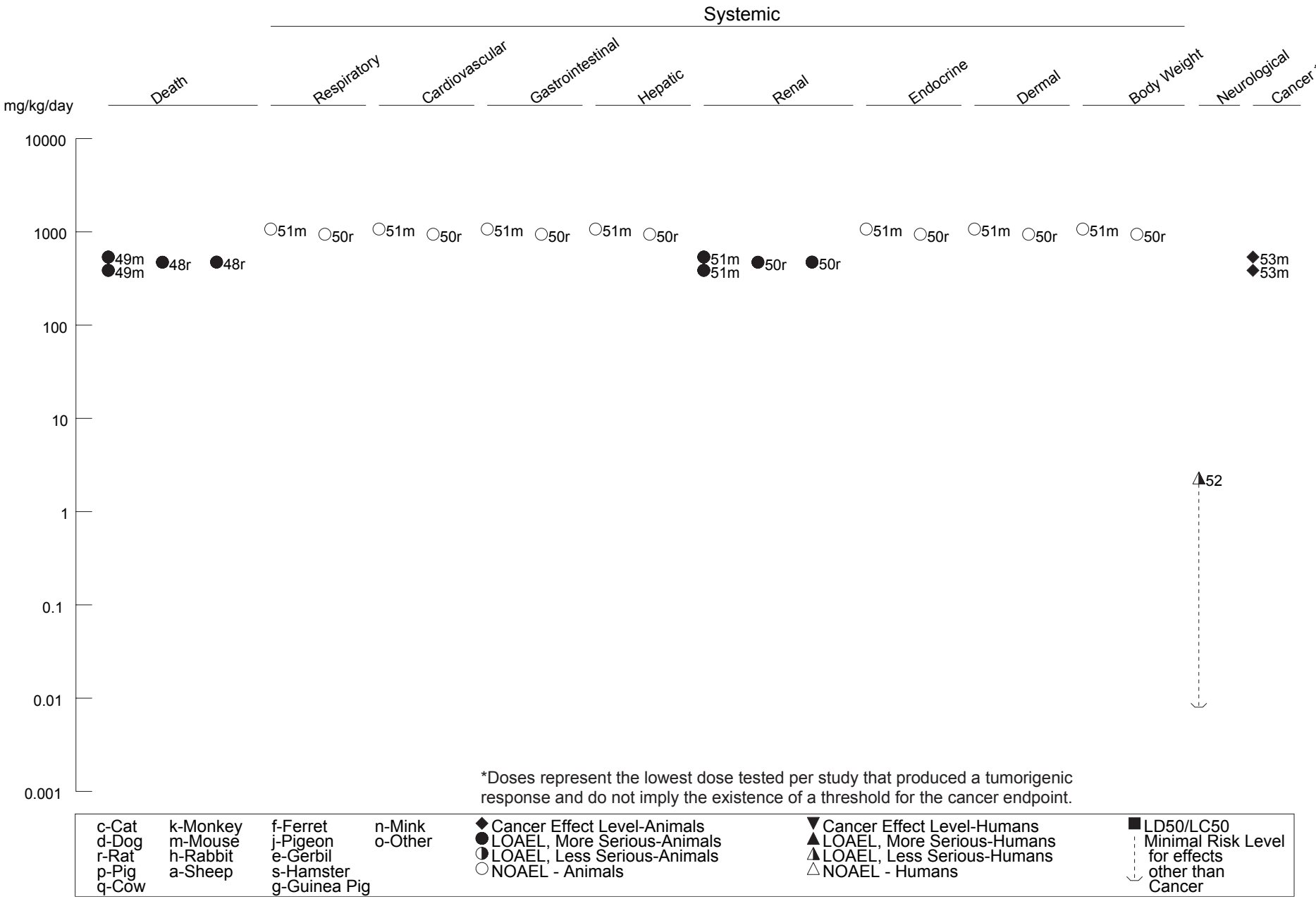


Figure 3-2 Levels of Significant Exposure to Tetrachloroethylene - Oral *(Continued)*

Chronic (≥365 days)



Gastrointestinal Effects. Vomiting has been reported in boys treated with unspecified oral doses of tetrachloroethylene to remove intestinal worms (Wright et al. 1937). Histological changes in the gastrointestinal tract were not observed in rats or mice treated by gavage with tetrachloroethylene for 78 weeks at doses that increased mortality (NCI 1977).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to tetrachloroethylene. In addition, the data on the hematologic effects of tetrachloroethylene in laboratory rodents exposed orally are limited to intermediate-duration studies in mice yielding uncertain findings.

In a 15-day study of male Swiss mice exposed to tetrachloroethylene in sesame oil via gavage dosing at 3,000 mg/kg/day, hematologic changes included significantly decreased hemoglobin (17% less than controls), hematocrit (23% lower), and erythrocyte (21%) and platelet counts (32%), as well as increased leukocyte count (42% higher than controls; Ebrahim et al. 2001).

Hemoglobin, hematocrit, and cell counts were not affected in rats exposed to tetrachloroethylene in drinking water (4% Emulphor) at doses up to 1,400 mg/kg/day for 90 days (Hayes et al. 1986). Mice exposed to 0.1 mg/kg/day tetrachloroethylene in drinking water for 7 weeks had high relative concentrations of tetrachloroethylene in the spleen, increased spleen weight, increased hemosiderin deposits and congestion of red pulp, increased serum LDH isozyme I, which was interpreted as being indicative of erythrocyte hemolysis, and a relative decrease in bone marrow erythropoiesis (Marth 1987). Milder or no hematological effects, depending on the parameters evaluated, occurred at exposures to 0.05 mg/kg/day. All hematological effects were reversible within an 8-week recovery period. There are several limitations of this study. First, only one sex of mouse was evaluated. Second, splenic hemosiderosis, one of the parameters evaluated, is present in normal mouse spleens; therefore, the presence of this pigment in the spleen is not necessarily an indicator of hemolysis unless it is more widespread and severe compared to control spleens. Third, grading of lesions by distribution and severity for either spleen or bone marrow was not documented in the paper. Fourth, the study author did not provide documentation that LDH isozyme I is the isozyme found in mouse erythrocytes.

Mild microcytic anemia occurred in B6C3F1 mice exposed via drinking water to tetrachloroethylene plus 24 other groundwater contaminants (Germolec et al. 1989). This study is discussed in more detail in Section 3.2.2.3.

Hepatic Effects. There is little information on the potential hepatic effects in humans exposed orally to tetrachloroethylene. Available information is limited to a single case report of obstructive jaundice and hepatomegaly reported in a 6-week-old infant exposed to tetrachloroethylene (1 mg/dL) via breast milk (Bagnell and Ellenberger 1977). After breast feeding was ended, a rapid improvement was observed.

The liver is a principal target organ in rodents exposed orally to tetrachloroethylene. Hepatic effects in rodents from oral exposure to tetrachloroethylene are similar to those produced by inhalation exposure. Mice are more sensitive than rats to tetrachloroethylene-induced toxic effects; these effects are related to tetrachloroethylene metabolism—particularly the formation of trichloroacetic acid—as discussed in Section 3.4. Hepatic effects in mice have occurred after acute- and intermediate-duration exposures to doses ≥100 mg/kg/day (Buben and O'Flaherty 1985; Schumann et al. 1980). Chronic-duration oral bioassays of tetrachloroethylene in rats and mice have been conducted (NCI 1977). No nonneoplastic hepatic lesions were observed, but these studies had significant limitations, as discussed further in Section 3.2.2.7.

Acute-duration studies have shown liver changes after only a single dose of tetrachloroethylene. Exposure of Swiss mice to 500 or 1,000 mg/kg/day tetrachloroethylene via gavage resulted in histopathology changes including centrilobular fatty degeneration and necrosis, with cytoplasmic vacuolization at the higher dose, after only 1 day of exposure (Philip et al. 2007). In this study, serum ALT was significantly increased (>2-fold) at exposures ≥150 mg/kg/day after 1 day of exposure. Tetrachloroethylene administered by gavage at a dose of 1,000 mg/kg/day for 10 days to male B6C3F1 mice increased relative liver weights and elevated cyanide-insensitive palmitoyl CoA oxidase levels, indicative of peroxisomal proliferation (Goldsworthy and Popp 1987). Schumann et al. (1980) reported hepatocellular swelling in mice given 11 daily gavage doses of 100 mg tetrachloroethylene/kg.

Liver weights were significantly increased and CYP2B P-450 enzymes were significantly induced in rats treated by gavage with tetrachloroethylene in corn oil at 1,000 and 2,000 mg/kg/day for 5 days (Hanioka et al. 1995). The P-450 enzymes were also significantly induced at 500 mg/kg/day, although no change in liver weight was noted at this dose. Phase II drug metabolizing enzymes were also induced with significant increases in DT-diaphorase activity at 2,000 mg/kg/day, significant increases in glutathione *S*-transferase activity at 1,000 and 2,000 mg/kg/day, and significant increases in uridine 5'diphosopho (UDP)-glucuronyltransferase activity at all doses tested (≥125 mg/kg/day). Tetrachloroethylene administered by gavage at a dose of 1,000 mg/kg/day for 10 days F344 rats did not elevate cyanide-

insensitive palmitoyl CoA oxidase levels significantly above controls, although relative liver weights were increased (Goldsworthy and Popp 1987). Schumann et al. (1980) observed no liver changes in rats given 11 daily gavage doses up to 1,000 mg/kg/day. Increased relative liver weights, increased serum ALT, and hepatocellular hypertrophy were observed in female rats treated by gavage with tetrachloroethylene in corn oil at a dose of 1,500 mg/kg/day for 14 days, but not at 500 mg/kg/day (Berman et al. 1995). Rajamanikandan et al. (2012) observed increased serum AST, ALT, and alkaline phosphatase, along with histopathology changes (minimal periportal lymphocytic infiltration, inflammation, and hepatocellular necrosis; incidences not reported) in female Wistar rats given 14 consecutive daily gavage doses of 1,000 mg/kg/day tetrachloroethylene. The authors also measured increased levels of hepatic lipid oxidation as well as decreased antioxidant levels (Rajamanikandan et al. 2012).

Similar liver effects are seen after intermediate-duration exposure to tetrachloroethylene. When male and female Swiss mice were given tetrachloroethylene via gavage in sesame oil at a dose of 3,000 mg/kg/day for 15 consecutive days, hepatic effects included increased relative liver weight (in the absence of body weight change), altered glycolytic and gluconeogenic enzyme activities, and focal necrosis with hydropic changes (Ebrahim et al. 1996). In a similar study, groups of four male Swiss mice received daily gavage doses of 150, 500, or 1,000 mg/kg/day for 1, 7, 14, or 30 consecutive days (Philip et al. 2007). Serum ALT was significantly increased (>2-fold) in all exposure groups after 1 and 14 days of exposure, but groups exposed for 30 days exhibited no difference from control in serum ALT levels. Histopathology changes observed after exposure to 500 or 1,000 mg/kg/day included centrilobular fatty degeneration and necrosis, with cytoplasmic vacuolization at the higher dose; these changes were less pronounced after 30 days of exposure than after 1 day (Philip et al. 2007). Toxic effects induced in male Swiss Cox mice given tetrachloroethylene by gavage at doses of 0, 20, 100, 200, 500, 1,000, 1,500, or 2,000 mg/kg/day for 6 weeks were increased relative liver weight and triglycerides beginning at 100 mg/kg/day, decreased glucose-6-phosphate and increased SGPT at 500 mg/kg/day, and hepatocellular lesions at ≥200 mg/kg/day. Lesions consisted of centrilobular hepatocellular hypertrophy, karyorrhexis, centrilobular necrosis, polyploidy, and hepatocellular vacuolization. All of these effects were present in the two dose groups examined histologically (200 and 1,000 mg/kg/day) (Buben and O'Flaherty 1985). Centrilobular necrosis and increased levels of protein and protein-bound carbohydrates were observed in the livers of rats treated by gavage with tetrachloroethylene in sesame oil at 3,000 mg/kg/day for 42 days (Ebrahim et al. 1995).

Exposure to gavage doses of 2,400 mg/kg/day tetrachloroethylene in corn oil for 32 days resulted in increased relative liver weights as well as increased levels of serum AST and ALT in female Wistar rats; no hepatic effects were seen in the group exposed to 600 mg/kg/day (Jonker et al. 1996). Elevated liver weights, relative to body weight but not brain weight, occurred in both sexes of Sprague-Dawley rats given 1,400 mg/kg/day tetrachloroethylene in drinking water for 13 weeks. While the serum enzyme, 5'-nucleotidase, was increased in females given 1,400 mg/kg/day and in males given 400 or 1,400 mg/kg/day, results of other biochemical measurements did not suggest a hepatotoxic effect. In addition, gross necropsy examination did not reveal any abnormalities in selected organs, including the liver (Hayes et al. 1986). The major limitation of this study was the lack of microscopic examination of livers.

Tetrachloroethylene has been tested for initiating and promoting activity in a rat liver foci assay (Story et al. 1986). Mean liver weights and/or liver-to-body weight ratios were significantly increased relative to the controls in partially hepatectomized adult male Osborne-Mendel rats (10/group) administered 995 mg/kg/day tetrachloroethylene by gavage in corn oil. In both the presence and absence of an initiator (30 mg/kg diethylnitrosamine), tetrachloroethylene (995 mg/kg/day) induced an increase in enzyme-altered foci (foci with increased GGT activity).

Chemically-related nonneoplastic liver lesions were not reported for Osborne-Mendel rats or B6C3F1 mice given tetrachloroethylene by gavage in a chronic bioassay (NCI 1977). This study, including its limitations, is discussed in Section 3.2.2.7.

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to tetrachloroethylene. Acute-duration studies measuring renal effects in animals have not used doses lower than 1,000 mg/kg/day. At this dose, male, but not female, rats exhibited renal changes characteristic of α-2u-globulin nephropathy (Berman et al. 1995; Goldsworthy et al. 1988; Potter et al. 1996), while male mice exhibited peroxisomal proliferation in the kidneys (Goldsworthy and Popp 1987). The lowest dose resulting in renal effects in intermediate-duration studies was 400 mg/kg/day; rats exposed to this dose for 90 days showed increased relative kidney weights (Hayes et al. 1986). In chronic oral studies, toxic nephropathy, which contributed to early mortality, was observed in both sexes of mice and rats at TWA doses ≥386 mg/kg/day; these studies had significant limitations, as discussed in Section 3.2.2.7.

Daily gavage administration of 1,000 mg/kg tetrachloroethylene to male F344 rats for 10 days produced an increase in protein droplet accumulation and cell proliferation in the P2 segment of the kidney. This

effect, not seen in female rats, was correlated with an increased presence of α-2μ-globulin in the proximal convoluted epithelial cells (Goldsworthy et al. 1988). Results from an earlier study by the same investigators indicated that peroxisomal proliferation in the rat kidney was not associated with administration of 1,000 mg/kg/day tetrachloroethylene (Goldsworthy and Popp 1987). Peroxisomal proliferation was the only end point investigated in this experiment. Male F344 rats receiving daily gavage doses of 1,000 mg/kg/day tetrachloroethylene in 4% Emulphor exhibited increased numbers of hyaline droplets in renal tubules, also consistent with α-2μ-globulin accumulation, after 1, 3, or 7 days of exposure (Potter et al. 1996). Kidney weight, renal cell proliferation rate, and frequency of DNA strand breaks in the kidney were not altered by exposure (Potter et al. 1996). Kidney effects were not observed in female rats treated by gavage with tetrachloroethylene in corn oil at a dose of 1,500 mg/kg/day for 14 days (Berman et al. 1995).

Male B6C3F1 mice exposed to 1,000 mg/kg/day by gavage for 10 days had peroxisomal proliferation, as evidenced by elevated cyanide-insensitive palmitoyl CoA oxidase levels (Goldsworthy and Popp 1987). Increased relative kidney weights (in the absence of body weight changes) were observed in male and female Swiss mice given gavage doses of 3,000 mg/kg/day tetrachloroethylene in sesame oil for 15 consecutive days (Ebrahim et al. 1996). Histopathology examination of the kidneys showed hypercellular glomeruli. In male Swiss mice given daily gavage doses of 150, 500, or 1,000 mg/kg/day for 1, 7, 14, or 30 consecutive days, cell proliferation was increased in the kidneys after 30 days of exposure, but no histopathology changes were seen, and no change in BUN was observed at any time point (Philip et al. 2007).

Male rats exposed to 1,500 mg/kg/day tetrachloroethylene by gavage for 42 days developed typical α-2μ-globulin nephropathy (Green et al. 1990). Male rats, but not female rats, also developed α-2μ-globulin nephropathy following daily gavage treatment with tetrachloroethylene at 500 mg/kg/day for 4 weeks (Bergamaschi et al. 1992). Exposure of female Wistar rats to gavage doses of 2,400 mg/kg/day tetrachloroethylene in corn oil for 32 days resulted in urinalysis changes including increased urine volume, and increased protein, GGT, ALP, LDH, and NAG excretion. Increased relative kidney weights were also noted, and histopathology examination revealed increased incidences of mild multifocal tubular vacuolation and karyomegaly. (Jonker et al. 1996). Rats exposed to a lower dose of 600 mg/kg/day did not exhibit renal effects (Jonker et al. 1996).

Hypercellular glomeruli and congestion of the convoluted tubules were observed in the kidneys of rats treated by gavage with tetrachloroethylene (3,000 mg/kg/day) in sesame oil for 42 days (Ebrahim et al.

1995). Significant increases in the levels of protein and protein-bound carbohydrates in the kidneys were also observed. No other doses of tetrachloroethylene were used in this study. Increased kidney/body weight ratios were observed in male rats treated with tetrachloroethylene in the drinking water at 400 mg/kg/day for 90 days (Hayes et al. 1986). No effects on the kidneys were observed at a dose of 14 mg/kg/day.

Osborne-Mendel rats and B6C3F1 mice of each sex were exposed to tetrachloroethylene in corn oil by gavage for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in a carcinogenicity bioassay (NCI 1977). TWA doses for the study were 536 and 1,072 mg/kg/day for male mice, 386 and 772 mg/kg/day for female mice, 471 and 941 mg/kg/day for male rats, and 474 and 949 mg/kg/day for female rats; untreated and vehicle control groups were included. Study limitations are discussed in Section 3.2.2.7. Toxic nephropathy occurred at all dose levels in both sexes of rats and mice, as did increased mortality. The nephropathy in both species was characterized by degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium and hyaline intraluminal casts. Rat kidneys also had occasional basophilic tubular cytomegaly, chronic inflammation, and mineralization.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to tetrachloroethylene, and few data are available in animals. Histopathological changes in the adrenal glands were not observed in female rats treated by gavage with tetrachloroethylene in corn oil at a dose of 1,500 mg/kg/day for 14 days (Berman et al. 1995). In a chronic bioassay, histological changes were not observed in the adrenal glands, thyroid, parathyroid, pancreas, or pituitary of rats and mice treated by gavage with tetrachloroethylene at doses that resulted in increased mortality (NCI 1977).

Dermal Effects. In family members of patients with leukemia from the Woburn study, 13 of 25 adults who had been chronically exposed to solvent-contaminated drinking water (including tetrachloroethylene) developed skin lesions. These were maculopapular rashes that occurred approximately twice yearly and lasted 2–4 weeks. These skin conditions generally disappeared within 1–2 years after cessation of exposure to contaminated water (Byers et al. 1988). There is no conclusive evidence that skin lesions were related to solvent exposure in general or to tetrachloroethylene specifically.

Few data on dermal effects after oral exposure are available in animals. In a chronic bioassay, histological changes were not observed in the skin of rats and mice treated by gavage with tetrachloroethylene at doses that resulted in increased mortality (NCI 1977).

Body Weight Effects. No studies of body weight effects in humans exposed to tetrachloroethylene were identified in the available literature. Body weight effects observed in studies of animals exposed orally are not consistent across study or species/strain of animal. At the end of a 5-day study, body weights of male Wistar rats treated by gavage with tetrachloroethylene at 2,000 mg/kg/day were 16% lower than controls (Hanioka et al. 1995). Body weight gain was decreased 22% in male F344 rats treated by gavage with tetrachloroethylene at 1,000 mg/kg/day for 11 days (Schumann et al. 1980). A decrease in body weight gain of approximately 25% was observed in pregnant F344 rats treated by gavage with tetrachloroethylene in corn oil at 900 mg/kg/day on gestation days 6–19 (Narotsky and Kavlock 1995). No effect on body weight was observed in F344 rats treated by gavage with tetrachloroethylene at 1,000 mg/kg/day for 7 or 10 days (Goldsworthy and Popp 1987; Potter et al. 1996), in female Wistar rats given gavage doses of 2,400 mg/kg/day tetrachloroethylene for 32 days (Jonker et al. 1996), in B6C3F1 mice treated by gavage with tetrachloroethylene at 1,000 mg/kg/day for 10 or 11 days (Goldsworthy and Popp 1987; Schumann et al. 1980).

In intermediate-duration studies, no effect on body weight was observed in male and female Swiss mice treated by gavage with tetrachloroethylene at 3,000 mg/kg/day for 15 days (Ebrahim et al. 2001), in female Wistar rats given gavage doses of 2,400 mg/kg/day tetrachloroethylene for 32 days (Jonker et al. 1996), or in Osborne-Mendel rats treated by gavage with tetrachloroethylene at doses ≤1,000 mg/kg/day for 6 weeks (NCI 1977). Hayes et al. (1986) reported 18 and 24% decreases in body weight gain in female Sprague-Dawley rats treated with tetrachloroethylene in the drinking water at 400 and 1,400 mg/kg/day, respectively, for 90 days. Body weight gain was significantly decreased (15%) in males only at 1,400 mg/kg/day. A 30% reduction in body weight gain was observed in female B6C3F1 mice treated by gavage with tetrachloroethylene at 562 mg/kg/day for 90 days (NCI 1977), but no effect on body weight gain in male mice was noted at this dose.

An explanation for the differences in effect on body weight in rats in the studies was not readily apparent; the differences do not appear to be related to strain or sex of the animals or to exposure duration. Changes in body weight in the available chronic-duration oral studies are also not consistent. Changes in body weight were not observed in Osborne-Mendel rats or B6C3F1 mice in a chronic bioassay at doses associated with increased mortality (up to 941 mg/kg/day for rats and 1,072 mg/kg/day for mice) (NCI 1977).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to tetrachloroethylene alone. The studies conducted to date were of exposure to mixed solvents and do not provide a clear picture of potential immunotoxic effects after oral exposure. Recent animal studies (Seo et al. 2008a, 2012) observed enhancement of antigen-stimulated allergic responses in rats and mice, and enhanced inflammation in rats, after exposure to very low oral doses of tetrachloroethylene (from 0.0009 to 0.09 mg/kg/day); however, the effects are of uncertain toxicological and human health relevance, as the degree of change that should be considered adverse is unclear.

There was, however, a study suggesting immunological effects in humans with chronic exposure to a solvent-contaminated domestic water supply. Several wells in Woburn, Massachusetts, were contaminated by a variety of solvents. The two main volatile chlorinated hydrocarbons measured before well closure were trichloroethylene (267 ppb) and tetrachloroethylene (21 ppb) (Byers et al. 1988). A potential association between water contamination in Woburn and cases of childhood leukemia is discussed in Section 3.2.2.7.

Some immunological abnormalities were found in 23 adults in Woburn who were exposed to contaminated water and who were family members of children with leukemia. These immunological abnormalities, tested for 5 years after well closure, were persistent lymphocytosis, increased numbers of T lymphocytes, and depressed helper:suppressor T cell ratio. A follow-up test 18 months later revealed reductions in lymphocyte counts, decreased numbers of suppressor T cells, and increased helper:suppressor ratio. Auto-antibodies, particularly anti-nuclear antibodies, were detected in 48% (11/23) of the adults tested. In the Woburn population, there was also a suggestion of an association between cumulative exposure to contaminated wells and increased urinary tract infections and respiratory disorders (asthma, bronchitis, pneumonia) in children (Lagakos et al. 1986).

Interpretation of the results reported by Byers et al. (1988) and Lagakos et al. (1986) is limited because of the possible bias in identifying risk factors for immunological abnormalities in a small, nonpopulation-based group identified through probands with leukemia. There is evidence that some genetic factor or factors may predispose persons to both altered immunologic parameters as well as an increased risk of developing leukemia. Other limitations of this study are described in Section 3.2.2.7.

Atrophy of the spleen and thymus, indicated by significantly decreased organ weights, was noted in rats treated by gavage with tetrachloroethylene in corn oil at 2,000 mg/kg/day for 5 days (Hanioka et al. 1995). This effect was not observed at 1,000 mg/kg/day. Histopathological changes in the spleen and thymus were not observed in female rats treated by gavage with tetrachloroethylene in corn oil at 1,500 mg/kg/day for 14 days (Berman et al. 1995).

Enhanced antigen-stimulated allergic responses have been demonstrated following small oral doses of tetrachloroethylene in both rats (Seo et al. 2008a) and mice (Seo et al. 2012). In addition, rats exposed to tetrachloroethylene displayed enhanced inflammatory responses (Seo et al. 2008a). Wistar rats and ICR mice were exposed to drinking water containing 0, 0.01, or 1 mg/L tetrachloroethylene for 2 or 4 weeks (estimated doses of 0, 0.0009, or 0.09 mg/kg/day in rats; 0, 0.0025, or 0.26 mg/kg/day in mice). Rats and mice were sensitized by intraperitoneal injection of anti-dinitrophenol IgE antibody 2 days or 1 day prior to the end of exposure, respectively. The passive cutaneous anaphylaxis (PCA) reaction was significantly increased in rats treated with 0.09 mg/kg/day and mice treated with 0.0025 and 0.26 mg/kg/day for 4 weeks, in a dose-dependent manner. Neither species demonstrated enhanced PCA reactions after exposure for 2 weeks. However, microscopic examination of skin demonstrated that all rats exposed for 2 weeks demonstrated increased lymphocyte infiltration (~1.2-fold more lymphocytes in treated groups compared with controls) and perivascular mast cell accumulation (~2-fold more). In addition, rats exposed to 0.09 mg/kg/day for 2 weeks demonstrated significantly increased (~1.3-fold) histamine release from antigen-stimulated peritoneal mast cells. These assays were not conducted following the 4-week exposure in rats or any exposure duration in mice. There was no treatment-related change in the relative weights of the spleen, thymus, and cervical lymph node of rats exposed for 4 weeks (not assessed at 2 weeks in rat or any duration in mice), but the relative mesenteric lymph node weight was significantly increased at both exposure levels. Microscopic examination of the mesenteric lymph nodes showed enlarged lymphoid nodules with clearly visible germinal centers; the study authors did not indicate the incidence or severity of this effect in the two treated groups.

Immunological effects were detected in a study exposing female B6C3F1 mice to drinking water containing tetrachloroethylene (maximum concentration 6.8 ppm) and 24 other contaminants frequently found in groundwater for 14 or 90 days (Germolec et al. 1989). Mice exposed to the highest concentration of this laboratory-prepared stock solution had a dose-related suppression in antibody plaque-forming units to sheep red blood cells and increased host susceptibility to infection by the protozoan, *Plasmodium yoelii*. There were no changes in lymphocyte number or T cell subpopulations, no alterations of T cell, natural killer cell or macrophage activities, and no effect on host susceptibility to

challenge with intravenous *Listeria monocytogenes* (bacteria) or PYB6 tumor cells. These findings indicate an immunotoxic effect on B cells/humoral immunity (Germolec et al. 1989). These effects cannot be attributed to tetrachloroethylene alone.

In a chronic bioassay, microscopic examination of the spleen, lymph nodes, and thymus of rats and mice exposed by gavage to tetrachloroethylene at doses that resulted in increased mortality did not reveal any adverse immunological or lymphoreticular effects (NCI 1977).

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects identified in rats for each duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Neurological Effects in Humans. Acute neurological effects in humans after ingesting tetrachloroethylene are similar to those seen after inhalation, such as dizziness, loss of coordination, and narcosis, in some cases leading to coma; however, available data are limited to a small number of case reports. A 6-year-old child who ingested 12–16 g of tetrachloroethylene was conscious upon admission to a hospital 1 hour after ingestion, but his level of consciousness deteriorated to somnolence and subsequently coma (Koppel et al. 1985). Other symptoms included drowsiness, vertigo, agitation, and hallucinations. The boy recovered completely.

The oral administration of tetrachloroethylene as an anthelminthic in humans was common at one time; however, newer therapeutic agents have since replaced tetrachloroethylene. Narcotic effects, inebriation, perceptual distortion, and exhilaration, but not death, were observed in patients receiving doses ranging from 2.8 to 4 mL (about 4.2–6 g) of tetrachloroethylene orally as an anthelminthic (Haerer and Udelman 1964; Kendrick 1929; Sandground 1941; Wright et al. 1937).

A series of retrospective cohort studies examining neurobehavioral and developmental end points as well as cancer was conducted on residents of Cape Cod, Massachusetts who were exposed to tetrachloroethylene leaching from the lining of vinyl-lined asbestos-cement water supply pipes (Aschengrau et al. 1998, 2003, 2008, 2009, 2011, 2012; Getz et al. 2012; Janulewicz et al. 2008, 2012; Paulu et al. 1999; Vieira et al. 2005). The exposure, discovered in 1980, had been occurring for the preceding 15 years; concentrations in the water in 1980 ranged from 1.5 to 7,750 µg/L. Exposure to other

water contaminants was considered by the study authors to be rare, limiting confounding by coexposures. Most of the studies examined effects in children who had been exposed *in utero* or during the first 5 years of life. In these studies, residential histories were obtained by questionnaire, and locations of affected pipes were collected from municipalities. Total exposure for each individual subject was then estimated as the total amount (in grams) of tetrachloroethylene delivered to the subject's residence by modeling leaching of tetrachloroethylene from the pipes and subsequent transport to households (using EPANET water distribution modeling software). The studies did not include estimates of tetrachloroethylene intake, as they considered information on water consumption and bathing habits obtained by questionnaire to be of limited reliability. Exposure to tetrachloroethylene in this cohort likely included oral, inhalation, and dermal routes, but oral exposure is considered to be the dominant exposure route.

Studies examining neurobehavioral end points of learning, attention, and behavior in the Cape Cod cohort were conducted (Janulewicz et al. 2008, 2012). Janulewicz et al. (2008) used parental questionnaires to compare academic difficulties, diagnoses of attention deficit disorder or hyperactive disorder, and behavioral problems among 1,910 exposed and 1,928 unexposed children whose mothers lived on Cape Cod during pregnancy or the first 5 years after birth. The results showed no differences in reported frequencies of learning, behavior, or attention difficulties in the groups exposed prenatally or during the early postnatal period (Janulewicz et al. 2008). A follow-up study examining neuropsychological end points in adults was performed (Janulewicz et al. 2012); participation in this study was very low, with only 35 exposed and 28 unexposed subjects agreeing to neuropsychological testing of original cohort. This study also reported no evidence of an association between exposure and neuropsychological tests for omnibus intelligence, academic achievement, or language end points using either crude analysis or multivariate analysis considering likely confounders (Janulewicz et al. 2012). Suggestive associations were noted between exposure and decrements in visuospatial functioning, learning and memory, motor speed, attention, and mood; however, the differences were not statistically significant (Janulewicz et al. 2012). The small group sizes in this study represent a significant limitation.

Aschengrau et al. (2011) examined the frequency of risky behaviors (including cigarette smoking, alcohol consumption, and drug use) during the teenage and young adult years among exposed and unexposed members of the cohort (exposure occurred during gestation and early childhood). A total of 831 exposed and 547 unexposed subjects with adequate information for exposure assessment provided information by questionnaire. For both smoking (relative risk 1.6; 95% CI 1.1–2.3) and alcohol use (relative risk 1.3; 95% CI 1.0–1.7), slight increases in relative risk were noted in the subjects whose exposure estimates were in the highest tertile; no increase in risk was seen for all exposed subjects or for those in lower

tertiles. A larger increase in relative risk was noted for association between drug use and tetrachloroethylene exposure; in the highest tertile, the relative risks were 1.6 (95% CI 1.2–2.2) for teen use of two or more illicit drugs, and 1.5 (95% CI 1.2–1.9) for adult use. The same subjects also responded to questions on mental illness, and results of this evaluation were published by Aschengrau et al. (2012). This study observed increased risks (1.5–2.1-fold increases) of bipolar disorder, post-traumatic stress disorder, and schizophrenia among exposed subjects, although the increases were not statistically significant. No increase in the risk for depression was observed. Among the subjects in the highest exposure tertile, a significant increase in the risk for bipolar disorder was observed (n=18 exposed cases; risk ratio 2.7; 95% CI 1.3–5.6 adjusted for covariates).

Getz et al. (2012) examined visual acuity, contrast sensitivity, and color discrimination in a small subset of the Cape Cod cohort (n=29 exposed and 25 unexposed) who agreed to vision testing. The testing revealed a nonsignificant decrease in contrast sensitivity and a significant increase in color confusion measured by the Farnsworth test (mean difference of 0.05; 95% CI 0.003–0.10) but not when measured by Lanthony's D-15d test. While limited by the small group sizes, the suggestive findings in this study are supported by studies of occupational and residential exposure to inhaled tetrachloroethylene that also observed decreased contrast sensitivity and color discrimination (Gobba et al. 1998; Schreiber et al. 2002; Storm et al. 2011; see Section 3.2.1.4).

Neurological Effects in Animals. Most of the limited available animal data on neurological effects of oral exposure to tetrachloroethylene comes from acute-duration studies; the lowest LOAEL in these studies was for suppression of operant behavior response in rats exposed to single gavage doses of 480 mg/kg (Warren et al. 1996). A single intermediate-duration study observed impairments in nociception and an increased threshold for seizure initiation in rats exposed to 5 mg/kg/day for 8 weeks (Chen et al. 2002). Chronic studies of effects on neurological function in animals exposed orally are not available.

When female Wistar rats received daily gavage doses of 2400 mg/kg/day tetrachloroethylene in corn oil in a 32-day study, severe but transient signs of central nervous system depression were noted immediately after dosing (Jonker et al. 1996). Ataxia was observed in pregnant rats treated by gavage with tetrachloroethylene in corn oil at 900 mg/kg/day on gestation days 6–19 (Narotsky and Kavlock 1995). The ataxia lasted about 4 hours after dosing. Four hours after female rats were given a single gavage dose of 1,500 mg tetrachloroethylene/kg, lacrimation and gait scores were significantly increased and motor

activity was significantly decreased (Moser et al. 1995). The study authors indicated that the effects were less 24 hours after dosing, but specific data were not provided.

A battery of neurological tests that examined autonomic, neuromuscular, and sensorimotor function, as well as activity and excitability, did not show any significant effects at 4 or 24 hours after a single gavage dose of 500 mg/kg, or 24 hours after the last of 14 daily doses of 1,500 mg tetrachloroethylene/kg (Moser et al. 1995). Operant response behavior was suppressed in male Sprague-Dawley rats tested immediately after a single gavage dose of 480 mg/kg tetrachloroethylene in polyethoxylated vegetable oil (Warren et al. 1996). The rats were trained for 2–3 weeks prior to dosing to press a lever for a milk reward. Rats exposed to 480 mg/kg tetrachloroethylene exhibited suppressed (4/6 rats) or nonexistent (2/6) operant responses after dosing. In the four rats that did respond, response rates returned to normal levels 15–30 minutes postdosing. No effect on operant response was noted in the group exposed to 120 mg/kg tetrachloroethylene (Warren et al. 1996).

A single intermediate-duration study of neurological effects in animals is available. Chen et al. (2002) observed impairments in nociception (increased latency to tail withdrawal from hot water and response latency to hot plate exposure) as well as an increased threshold for seizure initiation when male Sprague-Dawley rats were given gavage doses of 5 or 50 mg/kg/day tetrachloroethylene for 8 weeks (5 days/week). At the higher dose of 50 mg/kg/day, reduced locomotor activity was also observed.

In a chronic bioassay, microscopic examination of the brains of rats and mice exposed by gavage to tetrachloroethylene at doses that resulted in increased mortality did not reveal any adverse effects (NCI 1977).

The LOAELs for nervous system effects identified in human and animal studies and the NOAEL in rats are indicated in Table 3-3 and Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to tetrachloroethylene; data in animals are very limited.

Resorptions were significantly increased in rats treated by gavage with tetrachloroethylene in corn oil at doses of 900 and 1,200 mg/kg/day on gestation days 6–19 (Narotsky and Kavlock 1995). At

1,200 mg/kg/day, no live pups were delivered by gestation day 22, while the number at 900 mg/kg/day (5.2±1.5 pups/litter) was significantly ($p<0.01$) reduced compared to controls (7.7±0.7 pups/litter). The implantation sites required ammonium sulfide staining for detection, suggesting that the embryos died early in the treatment period. The 900 mg/kg/day dose also resulted in maternal ataxia and body weight gain approximately 25% less than controls.

In a chronic bioassay, microscopic examination of the testes and ovaries of rats and mice exposed by gavage to tetrachloroethylene at doses that resulted in increased mortality did not reveal any adverse effects (NCI 1977).

The serious LOAEL for reproductive effects in rats is recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

A large study of was conducted comparing birth weights and gestational ages of infants born to mothers who had lived in a Marine base housing area (Tarawa Terrace at Camp Lejeune, North Carolina) with a contaminated water supply well with infants of other housing areas on the base that did not receive contaminated water (Sonnenfeld et al. 2001). The well contamination was believed to originate from a dry cleaning facility near the well. Contaminants measured during the winter of 1985 in the affected supply well (not at the tap) at Camp Lejeune, North Carolina included tetrachloroethylene (1,580 ppb), trichloroethylene (57 ppb), 1,2-dichloroethylene (92 ppb), and vinyl chloride (27 ppb); the well was shut down shortly thereafter. Birth weight and gestational age were obtained from the review of birth certificates of 6,117 exposed and 5,681 unexposed infants, and mean difference in birth weight, OR for small-for-gestational-age, and preterm birth were assessed. The mean difference in birth weight was -26 g (90% CI -43–-9) when exposed and unexposed infants were compared. The OR for small-for-gestational age was 1.2 (90% CI 1.0–1.3). Similar results (data not reported) were observed after adjustment for potential confounders. No clear indication of an effect on preterm birth was seen. When the groups were stratified on maternal age and on number of prior fetal losses, a larger effect was seen among mothers ≥35 years old and among mothers who had two or more prior fetal losses; adjusted birth weight differences were -236 and -104 g, respectively, and adjusted ORs for small-for-gestational age were 2.1 and 2.5, respectively. The study authors suggested that the findings included a weak association between tetrachloroethylene exposure and small-for-gestational age, but no association with preterm birth or mean birth weight (Sonnenfeld et al. 2001). Limitations of the study include potential for exposure misclassification due to limited water sampling data, intermittent well use, and lack of information on

water use habits among exposed persons, as well as lack of control for potential confounders including maternal smoking and maternal height.

Aschengrau et al. (2008) examined birth weight and gestational duration among 1,353 exposed and 772 nonexposed members of the Cape Cod cohort exposed to tetrachloroethylene in drinking water (see Section 3.2.2.4 for further description of the cohort and exposure conditions). No association between exposure and birth weight or gestational duration was observed. A later study of congenital anomalies in the Cape Cod cohort (Aschengrau et al. 2009) observed increases in the adjusted ORs for all anomalies (OR 1.5; 95% CI 0.9–2.5) and specifically for neural tube defects (OR 3.6; 95% CI 0.8–14.0) and oral clefts (OR 3.2; 95% CI 0.7–15.0). The study authors noted that the results were limited by the small numbers of children with anomalies and the fact that the anomalies were identified by maternal report and not independently verified.

In the Woburn, Massachusetts, study of residents exposed to drinking water contaminated with solvents, including 21 ppb tetrachloroethylene, there was a suggestion that eye/ear anomalies and central nervous system/chromosomal/oral cleft anomalies were associated with exposure (Lagakos et al. 1986). However, several scientists have questioned the biological relevance of grouping these anomalies for purposes of statistical analysis (Lagakos et al. 1986). The association between birth outcome and drinking water contamination has also been examined in 75 towns in New Jersey (Bove et al. 1995). Based on four cases, oral cleft defects were increased (OR 3.54; 90% CI 1.28–8.78) in the group with the highest exposure (>10 ppb). Because of possible exposure misclassification and limits in the number of possible confounders that were examined (maternal occupational exposures, smoking, medical history, height, gestational weight gain), the study authors note that this study alone cannot resolve whether some of the relationships between drinking water contaminants and adverse outcome are causal or a result of chance or bias.

Increased numbers of postnatal deaths, and increased micro/anophthalmia were observed in offspring of rats treated by gavage with 900 mg/kg/day tetrachloroethylene in corn oil on gestation days 6–19 (Narotsky and Kavlock 1995). This dose also resulted in maternal toxicity (ataxia and body weight gain approximately 25% less than controls). On postnatal day 6, the number of pups/litter that were alive was 7.7±0.7 in the control litters, and 4.9±1.2 in the 900 mg/kg/day group ($p<0.001$; Narotsky and Kavlock 1995). Additional data about malformations were not provided.

In a study regarding late stages of nervous system development, male mouse pups were treated by gavage with tetrachloroethylene at 5 and 320 mg/kg/day for 7 days beginning at 10 days of age (Fredriksson et al. 1993). Throughout the dosing period, no clinical signs of toxicity were observed. Measures of activity (locomotion, rearing, and total activity) were completed in mice at 17 and 60 days of age. No significant effects were observed in mice at 17 days of age, while at 60 days of age, a significant increase in locomotion ($p<0.05$ or <0.01) and total activity ($p<0.01$) was observed at both doses.

All reliable LOAELs values identified in rats and mice are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.7 Cancer

The epidemiological data on cancers among humans exposed to tetrachloroethylene orally is much more limited than the inhalation data due to small numbers of studies and cohort sizes, as well as potential confounding by coexposure to other chlorinated solvents. Animal cancer bioassays were conducted in rats and mice exposed to tetrachloroethylene by gavage (NCI 1977); data in rats were not considered adequate for evaluation of carcinogenesis in rats due to premature mortality (NCI 1977), but hepatocellular tumors were observed in mice of both sexes.

An early case-control study was completed to examine the relationship between bladder cancer, kidney cancer, and leukemia among residents of Cape Cod with exposure to tetrachloroethylene in public drinking water (see Section 3.2.2.4 for description of the exposure circumstances and how exposure was assessed) (Aschengrau et al. 1993). Exposure was estimated as a relative delivered dose using a model described by Webler and Brown (1993). Based on a small number of cancer patients with tetrachloroethylene exposure (n=7), the investigators indicated that there was a tendency for an increased risk of leukemia among patients (n=2) who were most highly exposed. The small number of subjects limits the conclusions that can be drawn from this study.

Later studies of the Cape Cod cohort examined the risk of breast cancer (Aschengrau et al. 1998, 2003; Gallagher et al. 2011; Vieira et al. 2005). Studies by Aschengrau et al. (1998, 2003) examined cases of breast cancer diagnosed between 1983 and 1986 (n=258 cases and 686 controls from the same towns and matched on demographics) and between 1987 and 1993 (n=672 cases and 616 controls). When the data from the two studies were combined, an increased OR for breast cancer among women whose relative tetrachloroethylene dose was above the 75th percentile, when compared with unexposed women (adjusted

ORs of 1.6–1.9, depending on the number of years assumed for latency in the analysis). When an alternative exposure estimate took the reported water use habits of the participants into consideration (consumption of bottled water, shower and bathing frequency and duration) to estimate personal dose (Vieira et al. 2005), the results were similar to those obtained with the relative dose model originally used by Aschengrau (1998, 2003). Another update of the exposure assessment performed by Gallagher et al. (2011) added the use of water distribution modeling (using EPANET 2.0) and data smoothing to examine nonlinear associations between exposure and breast cancer. The revised exposure assessment yielded adjusted ORs of 1.0–1.7 for women in the highest exposure group (>90th percentile) for 0–19 years of latency; all of the CIs included 1.0. Taken together, the studies of the Cape Cod population suggest the possibility of a modest association between tetrachloroethylene in drinking water and breast cancer.

Paulu et al. (1999) presented the results of the case-control study for cancers other than breast cancer (including lung, brain, pancreas, and colon-rectum) in the Cape Cod population. No statistically significant associations were noted for any cancer type when comparing exposed and nonexposed participants, although nonsignificant increases in the OR for colon-rectum cancer were noted. A statistically significant increased OR for lung cancer (adjusted for confounders including smoking and gender) was noted among those subjects whose exposure level exceeded the 90th percentile (ORs ranged from 3.3 to 19.8, depending on the years of latency assumed).

In a study in New Jersey, tetrachloroethylene contamination of the drinking water was associated with an increased incidence of non-Burkitt's high-grade non-Hodgkin's lymphoma in females (Cohn et al. 1994). Many of the water supplies were also contaminated with trichloroethylene, making it difficult to assess the relative contribution of each chemical. The investigators also noted that the conclusions of their study are limited by potential misclassification of exposure because of lack of information on individual long-term residence and water consumption.

After trichloroethylene (212 µg/L) and tetrachloroethylene (180 µg/L) were identified in the drinking water supply of two towns in Finland, the incidence rates of total cancer, liver cancer, non-Hodgkin's lymphoma, multiple myeloma, and leukemia were compared with the rest of the country (Vartianinen et al. 1993). No significant difference was found. This study is limited in that people who might not have been exposed were included in the exposed group, and it is not clear how long the people were exposed. The contamination was discovered in 1992, and new sources of drinking water were supplied shortly after the discovery.

A controversial study of a population in Woburn, Massachusetts, reported a potential association between ingestion of drinking water contaminated with solvents and increased risk of childhood leukemia, particularly acute lymphocytic leukemia (Lagakos et al. 1986). However, numerous investigators (MacMahon 1986; Prentice 1986; Rogan 1986; Swan and Robins 1986) have evaluated the data and identified a number of shortcomings in the study. In addition, this population had coexposure to trichloroethylene and other solvents, so identification of effects attributable to tetrachloroethylene is not possible.

Cancer has been reported in experimental animals after oral exposure to tetrachloroethylene. Osborne-Mendel rats and B6C3F1 mice of each sex were exposed to tetrachloroethylene in corn oil by gavage for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in an NCI (1977) carcinogenicity bioassay. Because of numerous dose adjustments during the study, doses had to be represented as TWAs. TWA doses were 471 and 941 mg/kg/day for male rats, 474 and 949 mg/kg/day for female rats, 536 and 1,072 mg/kg/day for male mice, and 386 and 772 mg/kg/day for female mice. The elevated early mortality, which occurred at both doses in both sexes of rats and mice, was related to compound-induced toxic nephropathy (see Section 3.2.2.2). Because of reduced survival, this study was not considered adequate for evaluation of carcinogenesis in rats. Statistically significant increases in hepatocellular carcinomas occurred in the treated mice of both sexes. Incidences in the untreated control, vehicle control, low-dose, and high-dose groups were 2/17, 2/20, 32/49, and 27/48, respectively, in male mice, and 2/20, 0/20, 19/48, and 19/48, respectively, in female mice. Study limitations included control groups smaller than treated groups (20 versus 50), numerous dose adjustments during the study, early mortality related to compound-induced toxic nephropathy (suggesting that a maximum tolerated dose was exceeded), and pneumonia due to intercurrent infectious disease (murine respiratory mycoplasmosis) in both rats and mice.

Because of its carcinogenic activity in mouse liver, tetrachloroethylene has been tested for initiating and promoting activity in a rat liver foci assay. Tetrachloroethylene administered by gavage in corn oil at 995 mg/kg/day did not exhibit initiating activity as indicated by an increase in GGT-positive type I altered foci. Tetrachloroethylene did promote the appearance of type II altered foci, both in the presence and absence of an initiator (in this case, diethylnitrosamine) (Story et al. 1986).

All reliable CELs are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to tetrachloroethylene.

All five rabbits treated with a single dermal dose of 3,245 mg/kg tetrachloroethylene that was occluded for 24 hours survived (Kinkead and Leahy 1987). Additional studies regarding death following dermal exposure in animals were not located.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, or musculoskeletal effects in humans or animals after dermal exposure to tetrachloroethylene.

Cardiovascular Effects. Hypotension was reported in a male laundry worker found lying in a pool of tetrachloroethylene (Hake and Stewart 1977). In this case, the worker was exposed to tetrachloroethylene by both inhalation and dermal routes of exposure, and the exact contribution of dermal exposure is unknown. The patient fully recovered from the effects of tetrachloroethylene.

No studies were located regarding cardiovascular effects in animals after dermal exposure to tetrachloroethylene.

Hepatic Effects. Elevated serum enzymes (not further described) indicative of mild liver injury were observed in an individual found lying in a pool of tetrachloroethylene (Hake and Stewart 1977). Exposure in this case was by both the inhalation and dermal routes, and the exact contribution of dermal exposure is unknown.

No studies were located regarding hepatic effects in animals after dermal exposure to tetrachloroethylene.

Renal Effects. Proteinuria, which lasted for 20 days, was observed in an individual found lying in a pool of tetrachloroethylene (Hake and Stewart 1977). Exposure in this case was by both the inhalation and dermal routes, and the exact contribution of dermal exposure is unknown.

No studies were located regarding renal effects in animals after dermal exposure to tetrachloroethylene.

Dermal Effects. Five volunteers placed their thumbs in beakers of tetrachloroethylene for 30 minutes (Stewart and Dodd 1964). Within 5–10 minutes, all subjects had a burning sensation. After the thumb was removed from the solvent, the burning decreased during the next 10 minutes. Marked erythema, which cleared 1–2 hours after exposure, was present in all cases. Chemical burns characterized by severe cutaneous erythema, blistering, and sloughing have resulted from prolonged (more than 5 hours) accidental contact exposure to tetrachloroethylene used in dry cleaning operations (Hake and Stewart 1977; Ling and Lindsay 1971; Morgan 1969).

Rabbits were exposed dermally to pure tetrachloroethylene (2 mL/kg body weight), which was covered by an occlusive dressing for 24 hours to prevent evaporation of the chemical. The animals did not develop toxic signs, and skin lesions were not reported (Kinkead and Leahy 1987).

Ocular Effects. Intense ocular irritation has been reported in humans after acute exposure to tetrachloroethylene vapor at concentrations >1,000 ppm (Carpenter 1937; Rowe et al. 1952). Vapors of tetrachloroethylene at 5 or 20 ppm were irradiated along with nitrogen dioxide in an environmental chamber in order to simulate the atmospheric conditions of Los Angeles County. These conditions did not produce appreciable eye irritation in volunteers exposed to the simulated atmosphere (Wayne and Orcutt 1960).

No studies were located regarding ocular effects in animals after dermal exposure to tetrachloroethylene including direct application to the eye.

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals following dermal exposure to tetrachloroethylene.

3.2.3.4 Neurological Effects

A male laundry worker found lying in a pool of tetrachloroethylene was in a coma (Hake and Stewart 1977). The exposure to tetrachloroethylene in this case was by both the inhalation and dermal routes, and the exact contribution of dermal exposure is unknown. The patient fully recovered from the effects of tetrachloroethylene.

No studies were located regarding neurological effects in animals after dermal exposure to tetrachloroethylene.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after dermal exposure to tetrachloroethylene.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to tetrachloroethylene.

3.2.3.7 Cancer

No studies were located regarding cancer in humans after dermal exposure to tetrachloroethylene.

In a mouse skin initiation-promotion assay, tetrachloroethylene applied at amounts of 18 or 54 mg did not produce skin tumors over a 440–594-day study duration when applied either as an initiator or a promoter (Van Duuren et al. 1979).

3.2.4 Other Routes of Exposure

3.2.4.1 Immunological and Lymphoreticular Effects

Seo et al. (2008b, 2012) showed that tetrachloroethylene, administered intraperitoneally at 0.1 mg/kg in rats or ≥0.01 mg/kg in mice, significantly enhanced the PCA reaction in rats.

3.3 GENOTOXICITY

The results of *in vitro* and *in vivo* genotoxicity studies are summarized in Tables 3-4 and 3-5, respectively. Data from these assays indicate that tetrachloroethylene has the potential to be genotoxic. The lymphocytes of humans occupationally exposed to tetrachloroethylene showed no evidence of permanent chromosomal damage (sister chromatid exchange or chromosomal aberrations); however, DNA damage was observed in at least one assay (Tucker et al. 2011). In other *in vivo* assays (in rats,

Table 3-4. Genotoxicity of Tetrachloroethylene *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Bartsch et al. 1979; Emmert et al. 2006; Haworth et al. 1983; NTP 1986; Watanabe et al. 1998
Escherichia coli	Gene mutation	–	–	Greim et al. 1975; Henschler 1977
Lower eukaryotic system:				
Saccharomyces cerevisiae	Gene mutation	–	–	Bronzetti et al. 1983; Callen et al. 1980
S. cerevisiae	Recombination	(+/–)	–	Bronzetti et al. 1983; Callen et al. 1980; Koch et al. 1988
Mammalian cells:				
Fisher rat embryo cells	Cell transformation	+	NR	Price et al. 1978
BALB/C3T3 mouse cells		–	NR	Tu et al. 1985
		–	–	NTP 1986
Rat and mouse hepatocyte	DNA damage (unscheduled DNA synthesis)	–	NR	Costa and Ivanetich 1980
Human fibroblast cells	DNA damage (unscheduled DNA synthesis)	(+/–)	(+/–)	NIOSH 1980
Human lymphocytes	DNA damage	–	–	Hartman and Speit 1995
Human lymphocytes	Sister chromatid exchange	–	–	Hartman and Speit 1995
Chinese hamster ovary cells	Sister chromatid exchange	–	–	NTP 1986
Human MCL-5 cells (metabolically enhanced)	Micronucleus	NR	+	White et al. 2001
Chinese hamster lung cells	Micronucleus	–	–	Matsushima et al. 1999
Chinese hamster ovary (CHO-K1) cells	Micronucleus	NT	+	Wang et al. 2001

— = negative result; +/– = mixed results; + = positive result; DNA = deoxyribonucleic acid; NR = not reported; NT = not tested

Table 3-5. Genotoxicity of Tetrachloroethylene *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian cells:			
Human lymphocytes	Sister chromatid exchange	–	Ikeda et al. 1980; Seiji et al. 1990
Human lymphocytes	Chromosomal aberrations	–	Tucker et al. 2011
Human lymphocytes	DNA damage	+	Tucker et al. 2011
Human leukocytes and urine	DNA damage	–	Toraason et al. 2003
Rat/lymphocytes, liver, urine	DNA damage	–	Toraason et al. 1999
Mouse	DNA damage/induction of single strand breaks	+	Walles 1986
Mouse/hepatocytes	DNA damage	+/–	Cederberg et al. 2010
Mouse/kidney	DNA damage	–	Cederberg et al. 2010
Mouse/binding to or alkylation of liver DNA	DNA binding or alkylation	–	Schumann et al. 1980
Rat/binding of rat kidney DNA	DNA binding or alkylation	+	Mazullo et al. 1987
Mouse/binding of mouse liver DNA	DNA binding or alkylation	+	Mazullo et al. 1987
Rat, mouse/genetic damage in germinal system	Germ cell chromosome damage	–	NIOSH 1980
Rat, mouse/altered sperm morphology	Mutation in germ cells	(+/–)	NIOSH 1980
Mouse/reticulocytes	Micronucleus	–	Murakami and Horikawa 1995
Mouse/reticulocytes, before partial hepatectomy	Micronucleus	–	Murakami and Horikawa 1995
Mouse/reticulocytes, after partial hepatectomy	Micronucleus	+	Murakami and Horikawa 1995
Hot-mediated assays:			
Drosophila melanogaster/ sex-linked recessive lethal mutation	Gene mutation	–	NIOSH 1980; Valencia et al. 1985
Rat bone marrow cells	Chromosomal aberrations	–	NIOSH 1980
Human lymphocytes	Chromosomal aberrations	–	Ikeda et al. 1980
D. melanogaster/sex-linked recessive lethal mutation	Gene mutation	–	NTP 1986

– = negative result; + = positive result; (+/–) = mixed results; DNA = deoxyribonucleic acid

mice, and *Drosophila*), mixed results were shown for gene mutation, DNA binding and/or damage, chromosomal aberrations, and induction of micronuclei. An evaluation of the genotoxic potential of tetrachloroethylene *in vitro* suggests that tetrachloroethylene is unlikely to induce reverse mutations in *Salmonella typhimurium*; however, positive responses have been observed under some conditions (possibly due to metabolites and/or contaminants). Assays for chromosomal aberrations and DNA damage in mammalian cells have also shown mixed results, and most positive results required the presence of metabolic activation.

Assays in humans following occupational exposure to tetrachloroethylene via inhalation have not provided definitive evidence for clastogenic effects (Table 3-5). Increases in chromosome aberrations and sister chromatid exchanges were not detected in lymphocytes from 10 workers who were occupationally exposed to tetrachloroethylene (Ikeda et al. 1980). The exposure concentrations for these workers were estimated to be between 10 and 220 ppm for 3 months to 18 years. The small number of workers and the wide range of exposure concentrations and durations limit the generalizations that can be made from this study. Twenty-seven workers exposed to an 8-hour TWA concentration of 10 ppm tetrachloroethylene were compared to unexposed occupational controls with respect to incidence of sister chromatid exchanges (Seiji et al. 1990). Although the study authors had found no significant effect of cigarette smoking alone in either the exposed workers or the controls, the difference in sister chromatid exchange frequency between the exposed workers who smoked and the nonsmoking controls was statistically significant. The authors proposed a synergistic effect of chemical exposure and cigarette smoking. The number of workers examined was small (12 smokers and 2 nonsmokers among the exposed men; 9 smokers and 3 nonsmokers among the controls). The lack of any effect of cigarette smoking alone on the frequency of sister chromatid exchange is somewhat surprising, as this is a recognized effect that is well documented in the literature (Hook 1982).

In a study of 18 dry cleaning workers exposed to tetrachloroethylene at TWA concentrations >3.8 ppm for at least 1 year, no significant effect on the frequency of chromosome translocations in peripheral blood lymphocytes was observed in comparison to 18 control laundry workers (Tucker et al. 2011). Chromosomal damage was not significantly changed based on cigarette smoking or alcohol consumption. Evidence of transient chromosomal damage, namely increased frequencies of acentric fragments, was observed; TWA blood levels of tetrachloroethylene in dry cleaners significantly ($p=0.0026$) correlated with the frequency of these fragments. Although the sample sizes are small, no acentric fragments were observed in unexposed laundry workers. Using 8-hydroxydeoxyguanosine (8OHdG) as a marker for oxidative DNA damage and repair, Toraason et al. (2003) found no significant increase in DNA damage

in the leukocytes or urine of 18 dry cleaner workers (exposed to TWA concentration of tetrachloroethylene of 3.8 ppm) compared to 20 laundry workers. While there was an association between blood tetrachloroethylene levels and urinary 8OHdG ($r=0.4661$; $p<0.044$), there was no association between exposure indices and biomarkers after adjustments for age, body mass index, race, smoking status, and blood levels of antioxidants.

In vivo animal assays likewise showed mixed results for the induction of DNA damage or micronucleus formation. In male CD-1 mice administered tetrachloroethylene at 1,000 or 2,000 mg/kg/day via gavage for 2 days, there was equivocal evidence for the induction of DNA damage (Cederburg et al. 2010). In comet assays, a weak but significant and dose-related increase in tail intensity, but not tail moment, was reported in hepatocytes ($p=0.041$ in one-sided Jonckheere-Terpstra test); no significant effects associated with DNA damage were observed in the kidney. Although the study authors classified the response in the liver as "positive," these data, when analyzed in the context of biological relevance by the lab that conducted the experiment and by Lillford et al. (2010), Lovell (2010), and Struwe et al. (2011), were classified as "negative." The bases for classification of the response in the liver as negative included the small magnitude of the response, interanimal variability, the order of analysis of biological samples, responses that fell within the range of historical controls, and the lack of a statistical effect using other statistical tests (Dunnett's test for pairwise comparisons). Although induction of single-strand breaks in mouse liver and kidney DNA (but not in lung DNA) following intraperitoneal injection of 4–8 mmol tetrachloroethylene/kg body weight was reported in one study (Walles 1986), Toraason et al. (1999) found no significant increase in oxidative DNA damage (using 8OHdG as a biomarker) in the livers of rats administered a single intraperitoneal injection of tetrachloroethylene at up to 1,000 mg/kg. With respect to micronucleus induction, a single intraperitoneal injection of tetrachloroethylene given to mice at doses up to 2,000 mg/kg did not increase micronuclei in reticulocytes or hepatocytes when mice were treated before partial hepatectomy (Murakami and Horikawa 1995). Micronuclei were increased in hepatocytes at 1,000 and 2,000 mg/kg when mice were treated after partial hepatectomy. Additional *in vivo* studies showed no evidence of germ cell chromosomal damage and equivocal evidence of mutation in germ cells (positive in males, but not females, after one-time exposure only) of Sprague-Dawley rats exposed to tetrachloroethylene via inhalation for up to 5 days (NIOSH 1980).

In a study by Schumann et al. (1980), no DNA binding was observed in B6C3F1 mice exposed to tetrachloroethylene a single time via the inhalation or oral route of exposure. However, evidence of DNA binding of tetrachloroethylene in mouse liver and rat kidney was seen in experiments that utilized liver microsomes and the addition of glutathione transferases after a single intraperitoneal injection (Mazzullo

et al. 1987), providing some evidence that the glutathione metabolites of tetrachloroethylene may be mutagenic.

A large number of studies of *in vitro* genotoxicity of tetrachloroethylene have been performed using prokaryotic, eukaryotic, and mammalian cells (Table 3-4). Most of the studies using the Ames test with *S. typhimurium* have indicated that tetrachloroethylene itself is not a mutagen (Bartsch et al. 1979; Emmert et al. 2006; Haworth et al. 1983; NTP 1986; Watanabe et al. 1998). Several chlorinated aliphatic compounds identified in the spent liquor from the softwood kraft pulping process were found to be mutagenic (Kringstad et al. 1981). Tetrachloroethylene was one of several compounds isolated that was shown to be mutagenic for *S. typhimurium* TA1535 without the addition of liver microsomes for metabolic activation. In contrast, purified tetrachloroethylene was not mutagenic with or without exogenous metabolic activation. However, preincubation of tetrachloroethylene with purified rat liver GSH *S*-transferases in the presence of GSH and rat kidney fraction resulted in the formation of the conjugate, *S*-(1,2,2-trichlorovinyl)glutathione, which was unequivocally mutagenic in the Ames test (Vamvakas et al. 1989). Tetrachloroethylene oxide, an epoxide intermediate of tetrachloroethylene, was found to be mutagenic in bacterial studies (Kline et al. 1982).

Studies of mutagenicity on *Escherichia coli* have been negative (Greim et al. 1975; Henschler 1977), as have been tests for mitotic recombination in yeast (Callen et al. 1980; Koch et al. 1988). Mixed results were obtained in yeast when no metabolic activation was used in the experiments by Bronzetti et al. (1983). Koch et al. (1988) postulated that the lack of mutagenicity of tetrachloroethylene was because of its highly toxic effects on cells and that lower doses would be required to demonstrate unequivocally the presence or absence of mutagenic effects.

Direct effects on DNA by tetrachloroethylene have been investigated *in vitro* in several cell systems. Human fibroblasts were assayed for unscheduled DNA synthesis following exposure to tetrachloroethylene, but the results were equivocal (NIOSH 1980). This study is difficult to interpret because negative results were obtained using the higher concentrations, whereas the lower doses produced a weak positive response. In addition, the positive control chemicals (*N*-methyl-*N*-nitro-*N*-nitrosoguanidine, benz[a]pyrene) produced only weak positive responses. Other investigators found no effects on the DNA of rat and mouse hepatocytes or human lymphocytes (Costa and Ivanetich 1980; Hartman and Speit 1995). Most data do not support a directly mutagenic effect of tetrachloroethylene itself. The inconsistent results could be due to differences between tested species in metabolism or activation, protocol differences, or purity of the compound tested.

There are few data on clastogenic effects of tetrachloroethylene following *in vitro* exposure. When human lymphocytes and Chinese hamster ovary cells were assayed for sister chromatid exchanges, no increase in frequency was found (Hartman and Speit 1995; NTP 1986). Mixed results have been reported for micronucleus induction in human lymphocytes and Chinese hamster cell lines. There was no significant induction of micronuclei in Chinese hamster lung cells following exposure to tetrachloroethylene at up to 250 µg/mL in the presence or absence of metabolic activation (Matsushima et al. 1999). Wang et al. (2001) reported a dose-related, significant ($p<0.001$) increase in micronuclei in Chinese hamster ovary (CHO-K1) cells exposed to tetrachloroethylene at 63 ppm in a closed system. A dose-related increase ($p<0.05$) in micronuclei induction was likewise reported in human MCL-5 cells (metabolically enhanced to express human CYP enzymes) exposed to tetrachloroethylene at concentrations up to 2.0 mM (White et al. 2001). Two assays of cell transformation in mouse cells treated with tetrachloroethylene were negative (NTP 1986; Tu et al. 1985). However, Fischer rat embryo cells were transformed in the absence of metabolic activation (Price et al. 1978).

3.4 TOXICOKINETICS

Tetrachloroethylene is readily absorbed following inhalation and oral exposure as well as direct exposure to the skin. Pulmonary absorption of tetrachloroethylene is dependent on the ventilation rate, the duration of exposure, and at lower concentrations, the proportion of tetrachloroethylene in the inspired air. Compared to pulmonary exposure, uptake of tetrachloroethylene vapor by the skin is minimal. Once tetrachloroethylene is absorbed, its relatively high lipophilicity results in distribution to fatty tissue. The fat:blood partition coefficient in humans is in the range of 125–159. Because of its affinity for fat, tetrachloroethylene is found in milk, with greater levels in milk with a higher fat content. Tetrachloroethylene has also been shown to cross the placenta and distribute to the fetus.

Regardless of the route of exposure, only 1–3% of the absorbed tetrachloroethylene is metabolized to trichloroacetic acid by humans, and the metabolism of tetrachloroethylene is saturable. Compared to humans, rodents, especially mice, metabolize more tetrachloroethylene to trichloroacetic acid. Geometric mean V_{max} values for the metabolism of tetrachloroethylene of 13, 144, and 710 nmol/(minute/kg) have been reported for humans, rats, and mice, respectively. Trichloroacetic acid produced from tetrachloroethylene is excreted in the urine, and in humans, trichloroacetic acid excretion is linearly related to concentrations of tetrachloroethylene in air at levels up to about 50 ppm. Unmetabolized tetrachloro-

ethylene is exhaled. The half-lives of tetrachloroethylene in vessel-rich tissue, muscle, and adipose tissue of humans have been estimated to be 12–16, 30–40, and 55 hours, respectively.

A PBPK model for tetrachloroethylene toxicokinetics in mice, rats, and humans was published in Chiu and Ginsberg (2011); this model built upon previous PBPK models for tetrachloroethylene and for the related compound trichloroethylene.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

The primary route of human exposure to tetrachloroethylene is inhalation. In humans, tetrachloroethylene is readily absorbed into the blood through the lungs. The blood:gas partition coefficient of tetrachloroethylene in humans exposed for 4–6 hours to concentrations between 1 and 70 ppm ranged between 9.4 and 12.54 during exposure and between 15.74 and 23.65 after exposure (Chiu et al. 2007; Monster et al. 1979). Estimates of human blood:air partition coefficients from *in vitro* methods are shown in Table 3-6; in large part, these estimates are consistent with the *in vivo* values. *In vitro* blood:gas partition coefficients obtained by Mahle et al. (2004) suggest no gender- or age-related differences in partitioning between males and females or between pediatric and adult human blood.

Available data suggest that 64–100% of inhaled tetrachloroethylene is taken up from the lungs (Chiu et al. 2007; Monster et al. 1979). Pulmonary uptake of tetrachloroethylene is proportional to ventilation rate, duration of exposure, and at lower atmospheric concentrations of tetrachloroethylene, concentration of tetrachloroethylene in the inspired air (Hake and Stewart 1977; Stewart et al. 1981). In addition, a study of male volunteers showed higher total uptake of inhaled tetrachloroethylene with higher lean body mass; minute volume and adipose tissue did not influence uptake (Monster et al. 1979).

The rate of tetrachloroethylene uptake by the lungs is initially high, but decreases during exposure (Monster et al. 1979); this pattern is common for lipophilic compounds. The concentration of tetrachloroethylene in the venous blood of six male volunteers peaked near the end of a 6-hour exposure to 1 ppm, and declined thereafter (Chiu et al. 2007).

In another study (Pezzagno et al. 1988), 15 volunteers were exposed to tetrachloroethylene during periods of rest and during periods of rest alternated with periods of exercise. The experiments were designed to assess the relationship between pulmonary uptake and urinary concentration of tetrachloroethylene, and

Table 3-6. Partition Coefficients for Tetrachloroethylene in Mice, Rats, Dogs, and Humans

Partition coefficients[a]	Mouse	Rat	Dog	Human	Method[b]	Reference
Blood/air	16.9	18.9		10.3	Vial equilibration	Ward et al. 1988
Blood/air	21.5			11.6	Smear method	Gearhart et al. 1993
Blood/air		33.5		19.8	Smear method	Byczkowski and Fisher 1994
Blood/air		19.8			Intraarterial dosing	Dallas et al. 1994b
Blood/air		19.6	40.5		Oral dosing	Dallas et al. 1994a
Blood/air				16.67	Vial equilibration	Fisher et al. 1997
Blood/air					Vial equilibration	Mahle et al. 2004
males		12.8		15.8		
females				15.3		
Liver/air	70.3	70.3		70.3	Vial equilibration	Ward et al. 1988
Liver/air		62			Vial equilibration	Gearhart et al. 1993
Liver/air	48.8	50.2		61.1	Smear method	Gearhart et al. 1993
Liver/air		33.5			Vial equilibration	Mahle et al. 2004
Fat/air	2,060	2,300		1,638	Vial equilibration	Ward et al. 1988
Fat/air		1,237			Vial equilibration	Gearhart et al. 1993
Fat/air	1,510	1,437		1,450	Smear method	Gearhart et al. 1993
Fat/air		1,474			Vial equilibration	Mahle et al. 2004
Vessel-rich/air	70.3	70.3		70.3	Vial equilibration	Ward et al. 1988
Muscle/air	20.0	20.0		20.0	Vial equilibration	Ward et al. 1988
Muscle/air		18.1			Vial equilibration	Gearhart et al. 1993
Muscle/air	79.1	21.7		70.5	Smear method	Gearhart et al. 1993
Muscle/air		25.0			Vial equilibration	Mahle et al. 2004
Kidney/air		51.7			Vial equilibration	Gearhart et al. 1993
Kidney/air	79.1	51.3		58.6	Smear method	Gearhart et al. 1993
Kidney/air		30.6			Vial equilibration	Mahle et al. 2004
Brain/air		38.6			Vial equilibration	Mahle et al. 2004
Milk/air				59.27	Vial equilibration	Fisher et al. 1997
Liver/blood	2.3			5.28	Smear method	Gearhart et al. 1993
Liver/blood		1.9		6.83	Smear method	Byczkowski and Fisher 1994
Liver/blood		5.3			Intraarterial dosing	Dallas et al. 1994b
Liver/blood		5.0	2.4		Oral dosing	Dallas et al. 1994a
Fat/blood	70.4			125	Smear method	Gearhart et al. 1993
Fat/blood		42.4		159	Smear method	Byczkowski and Fisher 1994
Fat/blood		152			Intraarterial dosing	Dallas et al. 1994b
Fat/blood		150.5	71.4		Oral dosing	Dallas et al. 1994a
Muscle/blood	3.69			6.11	Smear method	Gearhart et al. 1993

Table 3-6. Partition Coefficients for Tetrachloroethylene in Mice, Rats, Dogs, and Humans

Partition coefficients[a]	Mouse	Rat	Dog	Human	Method[b]	Reference
Muscle/blood		3.0			Intraarterial dosing	Dallas et al. 1994b
Muscle/blood		2.4	2.4		Oral dosing	Dallas et al. 1994a
Kidney/blood	2.3			5.1	Smear method	Gearhart et al. 1993
Kidney/blood		4.5			Intraarterial dosing	Dallas et al. 1994b
Kidney/blood		3.2	2.1		Oral dosing	Dallas et al. 1994a
Lung/blood		2.5			Intraarterial	Dallas et al. 1994b
Lung/blood		1.9	1.3		Oral dosing	Dallas et al. 1994a
Brain/blood		4.4			Intraarterial dosing	Dallas et al. 1994b
Brain/blood		4.1	4.1		Oral dosing	Dallas et al. 1994a
Heart/blood		2.7			Intraarterial dosing	Dallas et al. 1994b
Heart/blood		2.4	2.4		Oral dosing	Dallas et al. 1994a
Milk/blood		12		2.80	Smear method	Byczkowski and Fisher 1994
Slowly perfused/ blood		0.93		7.8	Smear method	Byczkowski and Fisher 1994
Rapidly perfused/ blood		1.7		6.8	Smear method	Byczkowski and Fisher 1994
Perinatal/pediatric (pups, infants, children)						
Blood/air		24.3		8	Smear method	Byczkowski and Fisher 1994
Blood/air					Vial equilibration	Mahle et al. 2004
males		15.1		15.7		
females		15.8		15.7		
Liver/air					Vial equilibration	Mahle et al. 2004
males		42.2				
females		40.0				
Fat/air					Vial equilibration	Mahle et al. 2004
males		945.0				
females		1,014				
Muscle/air					Vial equilibration	Mahle et al. 2004
males		95.1				
females		126.7				
Kidney/air					Vial equilibration	Mahle et al. 2004
males		31.8				
females		30.6				
Brain/air					Vial equilibration	Mahle et al. 2004
males		28.9				
females		29.7				

Table 3-6. Partition Coefficients for Tetrachloroethylene in Mice, Rats, Dogs, and Humans

Partition coefficients[a]	Mouse	Rat	Dog	Human	Method[b]	Reference
Other tissues/ blood		4.5		6.6	Smear method	Byczkowski and Fisher 1994
Aged/elderly						
Blood/air		20.9			Vial equilibration	Mahle et al. 2004
Liver/air		65.9			Vial equilibration	Mahle et al. 2004
Fat/air		2,002			Vial equilibration	Mahle et al. 2004
Muscle/air		60.4			Vial equilibration	Mahle et al. 2004
Kidney/air		37.7			Vial equilibration	Mahle et al. 2004
Brain/air		58.3			Vial equilibration	Mahle et al. 2004

[a]Determined in tissue from adults except as noted

[b]Examples of partition coefficients for tetrachloroethylene determined by four methods:

(1) vial equilibration method: tetrachloroethylene was added to a closed vial containing blood or tissue and partitioning was determined by estimating the amount of chemical that disappeared from the head space after equilibration at 37°C.

(2) smear method (modification of the vial method): homogenized tissue was smeared onto the inside of a vial.

(3) intraarterial dosing: rats were given a single bolus injection of tetrachloroethylene through an arterial cannula. After treatment, groups of four rats were sacrificed at 1, 5, 10, 15, 30, and 60 minutes and at 2, 4, 6, 12, 36, 48, and 72 hours after dosing.

(4) oral dosing:rats and dogs were given a single oral dose of tetrachloroethylene. After treatment, groups of four rats were sacrificed at 1, 5, 10, 15, 30, and 60 minutes, and 2, 4, 6, 12, 8, 36, 48, and 72 hours after dosing, and groups of three dogs were sacrificed 1, 4, 12, 24, 48, and 72 hours after dosing.

between pulmonary uptake and ventilation and/or retention of the chemical. Urinary concentration of tetrachloroethylene was positively correlated with uptake of the chemical. The retention index decreased with increasing ventilation at rest and during exercise. The urinary concentration of tetrachloroethylene was ventilation and retention index-dependent, increasing when either of these two parameters increased. In the same study, a group of workers occupationally exposed to tetrachloroethylene (occupation not specified) were also monitored to determine if urinary concentration of tetrachloroethylene correlated with environmental exposure. A close relationship between the environmental TWA concentration and urinary concentration after a 4-hour exposure was found. These results suggest that physical activity affects the absorption of tetrachloroethylene and that these variations in absorption are reflected in urinary concentrations of the chemical.

Inhalation experiments in animals also indicate that tetrachloroethylene is readily absorbed through the lungs into the blood. Total recovery of radioactivity from expired air and urine was 90–95% when measured up to 72 hours after male Sprague-Dawley rats were exposed for 6 hours to 10 or 600 ppm tetrachloroethylene (Pegg et al. 1979). Dallas et al. (1994c) examined the uptake of tetrachloroethylene in Sprague-Dawley rats during nose-only exposure to tetrachloroethylene at 50 or 500 ppm for 3 hours. Near steady-state breath concentrations in exhaled air were achieved within about 20 minutes and were proportional to concentration (2.1–2.4 µg/mL at 500 ppm and 0.2–0.22 µg/mL at 50 ppm). The total uptake of tetrachloroethylene during the 3-hour exposure was 79.9 mg/kg at 500 ppm and 11.2 mg/kg at 50 ppm, indicating that cumulative uptake from the lungs was not proportional to inhaled concentration, possibly as a consequence of saturable metabolism (see Section 3.4.3).

3.4.1.2 Oral Exposure

Tetrachloroethylene was found in the blood of a 6-year-old boy who ingested 12–16 g of the compound, indicating that tetrachloroethylene is absorbed following oral exposure in humans (Koppel et al. 1985). The blood tetrachloroethylene level was 21.5 µg/mL 1 hour after ingestion.

Results from several studies (Dallas et al. 1994a, 1995; Frantz and Watanabe 1983; Pegg et al. 1979; Schumann et al. 1980) indicate that tetrachloroethylene is rapidly and virtually completely absorbed following oral administration to rats, mice, and dogs. Recovery of tetrachloroethylene from expired air and urine was 90.5–95% (up to 72 hours postdosing) in Sprague-Dawley rats given a single gavage dose of 1 or 500 mg/kg tetrachloroethylene in corn oil (Pegg et al. 1979). The peak blood tetrachloroethylene concentration of 40 µg/mL was measured 1 hour after dosing at 500 mg/kg tetrachloroethylene (Pegg et

al. 1979); the analytical technique used lacked the sensitivity to precisely measure blood levels following administration of 1 mg/kg tetrachloroethylene. In Sprague-Dawley rats and Beagle dogs given a single oral dose of tetrachloroethylene (10 mg/kg in polyethylene glycol 400) by gavage, the absorption constants were estimated to be 0.025/minute for rats and 0.34/minute for dogs (Dallas et al. 1994a). Maximum blood concentrations of tetrachloroethylene were reached 20–40 and 15–30 minutes in rats and dogs, respectively, after a single oral dose of tetrachloroethylene (1, 3, or 10 mg/kg) (Dallas et al. 1994a).

3.4.1.3 Dermal Exposure

Dermal absorption of tetrachloroethylene may occur with exposure to the vapor form as well as the liquid form. When volunteers' forearms and hands were exposed to tetrachloroethylene vapor (6.68 mmol/L) in a dynamic exposure chamber for 20 minutes, the concentration of tetrachloroethylene in exhaled air peaked approximately 45 minutes after exposure began (Kezic et al. 2000). The study authors estimated the tetrachloroethylene skin permeation rate to be 0.054 cm/hour. Dermal and pulmonary absorption of tetrachloroethylene vapor was compared by exposing subjects to the vapor (600 ppm) after they had been fitted with a full-facepiece respirator to prevent inhalation (Riihimaki and Pfaffli 1978). After an exposure period of 3.5 hours, absorption of tetrachloroethylene by the dermal route was found to be 1% of that expected had no respirator been worn.

Animal studies also indicate that dermal uptake of tetrachloroethylene following vapor exposure is minimal. For example, the skin absorption rate of tetrachloroethylene in nude Balb/cAnNCrj mice exposed to 200 ppm while wearing respirators was 0.002 mg/cm^2/hour (Tsuruta 1989). Skin absorption of tetrachloroethylene occurred by passive diffusion as defined by Fick's law and increased to 0.007 and 0.02 mg/cm^2/hour following exposures of 1,000 and 3,000 ppm, respectively. Tetrachloroethylene exposure (12,500 ppm) of F344 rats that were wearing respirators, and whose fur was closely clipped, indicated that <10% of a mixed inhalation dermal exposure to tetrachloroethylene vapor was taken up by the skin (McDougal et al. 1990).

Dermal uptake of liquid tetrachloroethylene may be enhanced by its lipophilic properties; lipophilic compounds may lead to defatting of the skin and disruption of the stratum corneum, increasing absorption. Dermal flux of neat liquid tetrachloroethylene was estimated to be 69 nmol/cm^2/minute in volunteers when each person's forearm skin (27 cm^2) was exposed to liquid tetrachloroethylene for 3 minutes (Kezic et al. 2001). The maximal rate of absorption, estimated based on measurements of tetrachloroethylene in expired air, occurred 20 minutes after the exposure began. Dermal absorption of

tetrachloroethylene in liquid form has also been measured by immersing one thumb of experimental subjects (about 0.1% of the total body surface area) into a liquid sample (99% pure tetrachloroethylene) and then measuring the concentration of tetrachloroethylene in the exhaled air (Stewart and Dodd 1964). A peak concentration of 0.31 ppm in exhaled air was reached after 40 minutes of exposure. Subjects in this study exhibited erythema and reported a burning sensation, indicating injury to the skin surface.

Application of undiluted tetrachloroethylene to the shaved backs of guinea pigs (strain not specified) resulted in blood concentrations of 1.1 µg/mL at the end of 30 minutes of exposure and 0.63 µg/mL at the end of 6 hours of exposure (Jakobson et al. 1982). The peak blood concentration of ~1.5 µg/mL tetrachloroethylene occurred approximately 30 minutes after the commencement of the 6-hour exposure (time-course data were not shown for the 30-minute exposure). The lower tetrachloroethylene blood level observed at the end of the longer exposure duration (6 hours) compared with the 30-minute exposure was attributed to local vasoconstriction of the exposed skin or rapid transport of the compound from the blood to adipose tissue.

Tetrachloroethylene applied in a volume of 0.5 mL to a 2.92 cm^2 patch of abdominal skin of ICR mice for 15 minutes yielded an estimated absorption rate of 24.4 nmol/minute/cm^2 (Tsuruta 1975). An *in vitro* study in which 1 mL of tetrachloroethylene was applied to 3.7 cm^2 of excised rat (SD-JCL) skin for 2–6 hours and penetration into a sodium chloride solution was measured resulted in an estimated penetration rate of 0.554 nmol/minute/cm^2 for tetrachloroethylene. The penetration rate estimated from the *in vitro* method was much slower than that observed *in vivo*. The authors suggested that the difference may result from the lower solubility of tetrachloroethylene in 0.9% sodium chloride compared to its solubility in body fluids (Tsuruta 1977).

Only one study examined uptake of tetrachloroethylene in an aqueous solution. Bogen et al. (1992) immersed anesthetized female hairless guinea pigs in water containing 27–64 ppb tetrachloro[14C]ethylene for 70 minutes, and the disappearance of radioactivity from the water was determined as a means of estimating dermal uptake. The guinea pigs were immersed up to their shoulders, and the top of the container was sealed around them to help prevent evaporation. About 20% of the radioactivity was lost from the water in an hour. When an animal was not present in the chamber, about 1.3% of the radioactivity was lost from the water. Therefore, it was assumed that most of the lost radioactivity was absorbed by the guinea pig. Over the concentration range studied, no difference in the dermal absorption of tetrachloroethylene was noted.

3.4.2 Distribution

Studies in animals, and autopsy findings in human cases of accidental death, demonstrate that absorbed tetrachloroethylene is distributed throughout the body regardless of the route of exposure, with highest concentrations measured in the adipose tissue, liver, and kidney (Dallas et al. 1994a, 1994b; Levine et al. 1981; Lukaszewski 1979; Pegg et al. 1979; Savolainen et al. 1977). Tetrachloroethylene has been shown to cross the placenta and distribute to the fetus and amniotic fluid of mice (Ghantous et al. 1986). In addition, tetrachloroethylene has been detected in goat's milk after oral exposure (Hamada and Tanaka 1995)

Organ:blood partition coefficients from *in vitro* and *in vivo* determinations can also inform the distribution of a chemical within the body. Organ:blood partition coefficients that exceed 1 suggest organs that can accumulate the compound of interest. Examples of organ:blood partition coefficients from experiments in four species are shown in Table 3-6. Regardless of the methods and in all species, partitioning from blood into fat was the greatest (partition coefficients ranged from 42.4 to 159), consistent with tetrachloroethylene's high lipophilicity. A marked species difference was observed in the milk:blood partition coefficients, which were reported to be 12 in Sprague-Dawley rats and 2.8 in humans (Byczkowski and Fisher 1994), possibly reflecting a greater fat content in the rat milk that was tested compared to the human milk.

3.4.2.1 Inhalation Exposure

Repeated inhalation exposure to tetrachloroethylene results in the accumulation of this compound in the body, as evidenced by increasing concentrations of tetrachloroethylene in expired air and blood. When experimental subjects were exposed by inhalation to 100 ppm tetrachloroethylene 7 hours/day for 5 days, the concentration of tetrachloroethylene in exhaled breath increased as the 5-day week progressed (Stewart et al. 1977). Following termination of exposure, additional accumulation of the compound was suggested by the prolonged decline (>14 days) in the concentration of tetrachloroethylene in exhaled air. The study authors suggested that tetrachloroethylene's affinity for fat tissue probably accounted for the protracted period of clearance from the lungs. Altmann et al. (1990) measured blood concentrations of tetrachloroethylene in volunteers before and after each of four daily 4-hour exposures to 10 or 50 ppm, as well as 1 day after the end of exposure. Even at these relatively air low concentrations and brief exposure durations, tetrachloroethylene levels in the blood increased from one exposure day to the next; blood levels increased from 36 to 56 µg/L after 1–4 days of exposure to 10 ppm, and from 59 to 153 µg/L after 1–4 days of exposure to 50 ppm tetrachloroethylene.

Autopsy data after accidental human poisonings have demonstrated distribution of inhaled tetrachloroethylene to various organs, including liver, kidney, brain, lung, and heart. The highest concentrations have generally been seen in the liver, kidney, and brain; however, the autopsy results did not include analysis of adipose tissue for tetrachloroethylene. In one human fatality due to tetrachloroethylene inhalation, the highest concentration of tetrachloroethylene was measured in the brain (36 mg/kg) and the lowest was in the lung (3 mg/kg) (Lukaszewski 1979). Tetrachloroethylene was detected in the liver (240 mg/kg), kidney (71 mg/kg), brain (69 mg/kg), and lung (30 mg/kg) of a dry cleaner who died following exposure to high concentrations of the chemical (Levine et al. 1981). Tetrachloroethylene concentrations were 79, 31, and 46 mg/kg in the brain, heart, and lungs, respectively, in a 2-year-old boy found dead shortly after he was placed in his room with curtains that had been incorrectly dry cleaned (Garnier et al. 1996). Tetrachloroethylene was measured in the liver and lung of a 26-year-old male found dead after intentional inhalation of a pressurized tire repair product containing tetrachloroethylene; concentrations were 341 mg/kg in the liver and 47 mg/kg in lung (Isenschmid et al. 1998). Tetrachloroethylene concentrations of 0.751 µg/g in muscle, 1.195 µg/g in kidney, 1.678 µg/g in myocardium, 1.855 µg/g in brain stem, and 1.95 µg/g in the liver were reported at autopsy of a 45-year-old woman who was found unconscious in a laundry area and was transported to the hospital where she subsequently died (Dehon et al. 2000).

Studies measuring radioactivity in animals after inhalation exposure to radiolabelled tetrachloroethylene confirm the distribution of tetrachloroethylene or its metabolites throughout the body, with the fat, liver, and kidney accumulating the highest concentrations. In rats exposed to 600 ppm tetrachloro-[1,2-14C]ethylene for 6 hours, the concentrations in kidney, liver, fat, lung, and heart were 0.167, 0.096, 0.082, 0.066, and 0.045 µmol eq/g, respectively, 72 hours after exposure; radioactivity was not detected in the brain or adrenal glands (Pegg et al. 1979). The distribution of the compound in Sprague-Dawley rats following exposure to 200 ppm tetrachloroethylene vapor (four daily 6-hour periods followed by 1 day of exposure for 0, 2, 3, 4, or 6 hours) was characterized by Savolainen et al. (1977). Tetrachloroethylene was found to have distributed primarily to perirenal fat. In rats receiving five 6-hour exposures, concentrations of tetrachloroethylene in perirenal fat, liver, cerebrum, and lungs were 1,724.8, 160.7, 142.5, and 74.0 nmol/g (Savolainen et al. 1977). Dallas et al. (1994b) exposed Sprague-Dawley male rats to tetrachloroethylene at 500 ppm for up to 2 hours. At specified times during and after exposure (up to 72 hours after exposure), groups of five rats were sacrificed and tetrachloroethylene residues in the perirenal fat, brain, liver, kidneys, heart, lung, skeletal muscle and blood were measured. The maximum tetrachloroethylene concentration measured at any time point in these tissues were 1,536.3, 173.9, 152.4,

107.5, 106.6, 94.6, 87.3, and 44 µg/g (respectively). Half-lives for elimination from these tissues ranged from 322 minutes in the blood to 578 minutes in fat. High levels of radioactivity were also observed in maternal body fat, brain, nasal mucosa, blood, and in well-perfused organs such as the liver, kidneys, and lungs (concentrations were not reported) when pregnant 657BL/6N mice were exposed to radiolabelled (14C) tetrachloroethylene for 10 minutes or 1 hour (Ghantous et al. 1986). The exposure concentration was not reported; 100 µCi of tetrachloroethylene was dissolved in oil and heated to generate the exposure.

The Ghantous et al. (1986) study in pregnant mice also showed that tetrachloroethylene can cross the placenta and distribute to the fetus and amniotic fluid. Unmetabolized tetrachloroethylene (measured as volatile radioactivity) was detected in the fetoplacental unit following inhalation exposure of pregnant 657BL/6N mice to radiolabelled (14C) tetrachloroethylene for 10 minutes or 1 hour (Ghantous et al. 1986). Nonvolatile radioactivity, measured to approximate the proportion of metabolized tetrachloroethylene, was higher in fetuses sacrificed later in gestation than those sacrificed early, consistent with increasing maternal metabolism of tetrachloroethylene over time.

3.4.2.2 Oral Exposure

Pertinent data regarding the distribution of tetrachloroethylene in humans following oral exposure were not found in the available literature.

The distribution of tetrachloroethylene in animals exposed orally is similar to that seen after inhalation exposure, with highest levels seen in the fat, liver, and kidneys. Distribution to the fat occurs over a long time period, while peak concentrations in liver and kidneys generally occur more rapidly. When male Sprague-Dawley rats were given single gavage doses of 1 or 500 mg/kg 14C-labelled tetrachloroethylene, radioactivity was found in the fat, kidney, liver, lung, and heart, but not the brain (Pegg et al. 1979). At the higher dose of 500 mg/kg, the concentrations were 0.272, 0.137, 0.097, 0.092, and 0.051 µmol eq/g in kidney, liver, fat, lung, and heart, respectively, at sacrifice 72 hours after exposure (Pegg et al. 1979). Following oral exposure of Sprague-Dawley rats to a single dose of tetrachloroethylene (10 mg/kg), the highest concentrations were found in the fat, liver, kidney, and brain (peak concentrations were 36, 12.3, 4.4, and 5.1 µg/g tetrachloroethylene, respectively; Dallas et al. 1994). Peak concentrations in the liver, kidney, and brain were reached 10–15 minutes after dosing, while the peak concentration in fat occurred 360 minutes after dosing (Dallas et al. 1994a). In Beagle dogs given a single oral dose of tetrachloroethylene, the highest concentrations were found in the fat, brain, liver, heart, and kidneys; peak concentrations were 42.8, 11.3, 6.3, and 4.9 µg/g, respectively (Dallas et al. 1994a). Except for the fat, in

which the peak concentrations were noted at 720 minutes, peak concentrations in the other organs were observed at 60 minutes, the first measurement time; the study authors suggested that true maximum concentrations may have actually occurred earlier.

3.4.2.3 Dermal Exposure

Pertinent data regarding the distribution of tetrachloroethylene in humans and animals following dermal exposure to the compound were not found in the available literature.

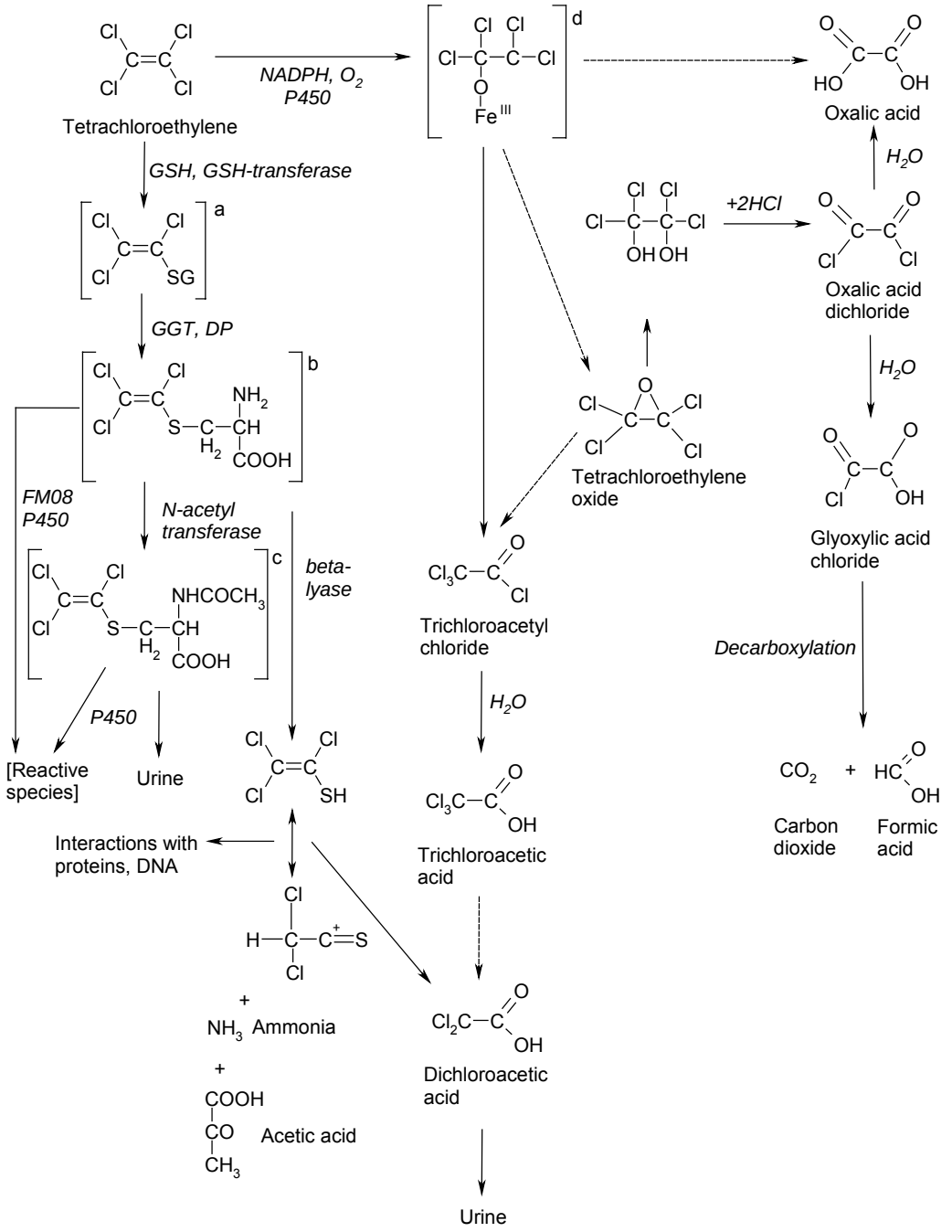
3.4.3 Metabolism

The metabolism of tetrachloroethylene has been reviewed by Chiu and Ginsberg, (2011), Chiu et al. (2007), and Lash and Parker (2001); the proposed metabolic pathways for tetrachloroethylene is depicted in Figure 3-3. Tetrachloroethylene is metabolized through two irreversible pathways in humans, rats, and mice: oxidation by cytochrome P-450 isozymes and glutathione conjugation via glutathione-S-transferase. Qualitatively, the metabolism is similar in humans, rats, and mice; however, the extent of metabolism, as well as the predominant pathway, varies by species and exposure route, with evidence for dose-dependency as well.

Oxidative metabolism is postulated to occur in the liver, lung, and kidney (Chiu and Ginsberg 2011). The primary isozyme believed to be responsible for oxidation of tetrachloroethylene is CYP2E1, based on data for similar compounds, but other isozymes may also be involved (Lash and Parker 2001). Oxidation of tetrachloroethylene is believed to yield a Fe-O intermediate, which is converted to trichloroacetyl chloride and then hydrolyzed to trichloroacteic acid (Chiu and Ginsberg 2011). An epoxide intermediate, initially believed to be the progenitor to trichloroacetic acid, was shown to decompose to ethandioyl dichloride and then to CO and CO_2 (Chiu and Ginsberg 2011); the epoxide pathway is believed to be minor. Oxalic acid has been observed to be a metabolite of tetrachloroethylene oxidation and may occur via either the epoxide or Fe-O intermediates. The urinary metabolites of tetrachloroethylene are trichloroacetic acid and dichloroacetic acid. These metabolites are considered to be the proximate toxicants responsible for the liver toxicity and carcinogenicity seen in tetrachloroethylene-exposed mice (Buben and O'Flaherty 1985; Chiu and Ginsberg 2011; Lash and Parker 2001).

Glutathione conjugation is proposed to occur primarily in the liver and kidney (Chiu and Ginsberg 2011). Glutathione conjugation of tetrachloroethylene produces trichlorovinyl glutathione and subsequently, S-trichlorovinyl-L-cysteine (TCVC) (Chiu and Ginsberg 2011; Lash and Parker 2001). TCVC may be

Figure 3-3. Proposed Pathways for the Metabolism of Tetrachloroethylene



[a]*S*-(1,2,2-trichlorovinyl)glutathione
[b]*S*-(1,2,2-trichlorovinyl)cysteine
[c]*N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine
[d]tetrachloroethylene-Fe-O intermediate

DP = dipeptidase; FM08 = flavin mono-oxygenase-3; GGT= gamma-glutamyl transpeptidase
Dashed lines indicate hypothesized or quantitatively minor pathways.

Source: adapted from Chiu and Ginsberg 2011; Dekant et al. 1986; Green et al. 1990; Pegg et al. 1979

bioactivated to reactive species via beta-lyase or flavin-containing monooxygenases (Anders et al. 1988; Krause et al. 2003). Dichloroacetic acid, which may also be formed via dechlorination of trichloroacetic acid, is postulated to occur primarily as an end product of beta-lyase activation after glutathione conjugation of tetrachloroethylene (Volkel et al. 1998). TCVC may also be N-acetylated to N-acetyl trichlorovinyl cysteine (NAcTCVC). NAcTCVC may be converted to reactive species via CYP3A sulfoxidation or excreted in the urine (Werner et al. 1996). Reactive metabolites in the kidneys produced via the glutathione conjugation pathway may play a role in the renal toxicity and carcinogenicity in tetrachloroethylene-exposed rats (Chiu and Ginsberg 2011; Lash and Parker 2001).

In humans, irrespective of the route of exposure, most (>80%) of the absorbed dose of tetrachloroethylene is exhaled unchanged (see Section 3.4.4). The major urinary metabolite in exposed humans is trichloroacetic acid; in three male and three female volunteers exposed to 10, 20, or 40 ppm tetrachloroethylene for 6 hours, cumulative excretion of trichloroacetic acid was 100-fold higher than cumulative excretion of the second major urinary metabolite, NacTCVC (Volkel et al. 1998). No dichloroacetic acid was detected in human urine. In this study, the elimination half-life in humans was 45.6 hours for trichloroacetic acid and 14.1 hours for NAcTCVC; the authors noted that the NAcTCVC was eliminated within 24 hours after exposure in all subjects.

Small amounts of *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine were detected in the urine of four workers occupationally exposed to tetrachloroethylene at 50 ppm for 4 or 8 hours/day, 5 days/week (Birner et al. 1996). The concentrations of *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine were 2.2–14.6 pmol/mg creatinine compared to concentrations of 13–65 nmol/mg creatinine for trichloroacetic acid and trichloroethanol combined. The amount of tetrachloroethylene exhaled was not determined, so it is not possible to estimate what percentage of the total dose of tetrachloroethylene was metabolized to *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine. Voelkel et al. (1999) also detected *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine in the urine of exposed humans.

Trichloroethanol has been reported to occur in the urine of workers exposed to tetrachloroethylene (Birner et al. 1996; Monster 1986); however, in studies of controlled exposure to pure tetrachloroethylene in humans or animals, trichloroethanol has not been detected in the urine (Buben and O'Flaherty 1985; Hake and Stewart 1977; Monster et al. 1979; Volkel et al. 1998).

The metabolism of tetrachloroethylene appears to be saturable in humans at high concentrations (>100 ppm), although the data are limited. Total measured trichloro-compounds in the urine of

tetrachloroethylene-exposed workers in dry cleaning and textile-processing plants reached a plateau in the urine at tetrachloroethylene exposure concentrations >100 ppm in workroom air (Ohtsuki et al. 1983). Another study of dry cleaning workers showed that the urinary level of trichloro-compounds was linearly related to exposure at concentrations <112 ppm (Seiji et al. 1989). Volkel et al. (1998) also observed a linear relationship between urinary excretion of trichloroacetic acid and NAcTCVC in humans exposed to 10, 20, or 40 ppm tetrachloroethylene for 6 hours, indicating that metabolic saturation did not occur at these low concentrations.

Biological monitoring data in occupationally exposed groups have indicated that the amount of tetrachloroethylene metabolized varies among different ethnic human populations; this finding is supported by a limited volunteer study. Seiji et al. (1989) reported that the relationship between total urinary trichloro-compounds and the concentration of tetrachloroethylene in breath air was 0.063 mg trichloroacetic acid/L per ppm tetrachloroethylene in Chinese workers, while the value was 0.7 mg trichloroacetic acid/L per ppm tetrachloroethylene in Japanese workers. Jang et al. (1993) determined that the biological exposure index in Korean workers exposed to 50 ppm tetrachloroethylene was 1.6 mg tetrachloroethylene/L in blood and 2.9 mg trichloroacetic acid/L in urine compared to the American Conference of Governmental Industrial Hygienists (ACGIH) values of 1 mg tetrachloroethylene/L in blood and 7 mg trichloroacetic acid/L in urine for exposure to 50 ppm (ACGIH 1991). In a controlled exposure experiment evaluating ethnic differences, a 35% higher peak urinary trichloroacetic acid concentration and significantly ($p<0.05$) higher area under the urinary trichloroacetic acid concentration-time curve were observed in three Caucasian volunteers compared with three Asian volunteers exposed to 50 ppm tetrachloroethylene for 6 hours (Jang et al. 1997). Blood concentrations of parent compound measured at the end of exposure did not differ between the two groups.

The variability of tetrachloroethylene metabolism among humans is reflected by a wide range of V_{max} and K_m values that have been reported in the literature, as shown in Table 3-7.

Species variability in metabolic rates is evident from the Vmax values for humans, rats, and mice (Table 3-7), which show that rats metabolize tetrachloroethylene at a greater rate than humans, and mice metabolize tetrachloroethylene at a much greater rate than rats. In a study comparing metabolism of tetrachloroethylene in humans and rats exposed to the same concentrations (10, 20, and 40 ppm) for 6 hours, the blood levels of trichloroacetic acid were much higher (20- and 10-fold higher immediately after exposure to 10 and 40 ppm, respectively) in rats than in humans. In addition, elimination half-lives of trichloroacetic acid and NAcTCVC in urine were much lower (11 and 7.5 hours, respectively) in rats

Table 3-7. Metabolism of Tetrachloroethylene in Mice, Rats, and Humans

Parameters	Human	Mouse	Rat
Total tetrachloroethylene metabolism[a]			
V_{max}/body weight (nmol/(minute/kg))	5.0–61 [13 (2.0)]	210–1860 [710 (2.04)]	27.2–400 [144 (2.97)]
K_m (nmol/mL blood)	1.2–193 [13 (5.1)]	1.6–32 [9.4 (2.95)]	1.8–108 [21 (4.57)]
$V_{max}/(K_m$ body weight)[b] (mL blood/(minute/kg))	0.05–9.3 [0.74 (4.3)]	12–248 [75 (2.57)]	3.7–15 [6.9 (1.69)]
In vitro liver cytosolic metabolism of tetrachloroethylene[c]			
Rate (pmol/minute/mg protein)	2.08±2.57	19.26±1.33	3.87±2.12
In vitro liver cytosolic GSH conjugation of tetrachloroethylene			
Rate (pmol/minute/mg protein)[d]	Not detected	3.4	18.2
In vitro liver cytosolic GSH conjugation of tetrachloroethylene to *S*-(1,2,2-trichlorovinyl)glutathione			
V_{max} (pmol/minute/mg protein)[e], male	Not detected	27.9±6	84.5±12
V_{max} (pmol/minute/mg protein)[e], female	Not detected	26.0±4	19.5±8
In vitro kidney cytosolic GSH conjugation of tetrachloroethylene to *S*-(1,2,2-trichlorovinyl)glutathione			
V_{max} (pmol/minute/mg protein)[e], male	Not detected	11.6±6	Not detected
V_{max} (pmol/minute/mg protein) [e], female	Not detected	12.2±4	Not detected
In vitro kidney cytosolic metabolism of *S*-(1,2,2-trichlorovinyl)-L-cysteine (β-lyase activity)[d]			
K_m (mM), male	2.53±0.09	5.69±2.22	0.68±0.06
K_m (mM), female	2.67±2.11	4.43±1.42	1.26±0.21
V_{max} (nmol/minute/mg protein), male	0.49±0.07	1.15±0.31	4.00±0.11
V_{max} (nmol/minute/mg protein), female	0.64±0.54	1.66±0.27	3.64±0.41
V_{max}/K_m, male	0.21	0.20	5.88
V_{max}/K_m, female	0.24	0.37	2.88

[a]Summarized by Hattis et al. (1990); values are range [geometric mean (geometric standard deviation)]
[b]Indicator of intrinsic low-dose metabolic clearance rate.
[c]From Reitz et al. 1996; values are means±standard deviations.
[d]From Green et al. 1990; values are means or means±standard deviations.
[e]From Dekant et al. 1998; values are means or means±standard error of the mean.

GSH = glutathione

than in humans (45.6 and 14.1 hours, respectively) (Volkel et al. 1998). Unlike humans, rats also excreted detectable levels of dichloroacetic aid in the urine, with an elimination half-life similar to that for trichloroacetic acid (11 hours).

Levels of an *N*-acetylcysteine glutathione conjugate detected in the urine of Wistar rats and NMRI and B6C3F1 mice and in the bile of F344 rats exposed to tetrachloroethylene were higher in rat urine than in mouse urine, and higher after gavage dosing than after inhalation exposure (Dekant et al. 1986; Green et al. 1990). The glutathione pathway was found to be minor at low doses, but began to increase following saturation of the cytochrome P-450 pathway (Green et al. 1990). Green et al. (1990) compared the activities of the glutathione S-transferase and β-lyase enzymes in humans, B6C3F1 mice, and F344 rats (Table 3-7). Glutathione conjugation to tetrachloroethylene could not be detected using liver cytosol from humans, while the rate of glutathione conjugation was higher in rat relative to mouse liver cytosol. β-Lyase activity in kidney cytosol was also higher in rats relative to mice and humans.

Urinary oxalic acid accounted for 18.7 and 6% of the dose following inhalation exposure of Sprague-Dawley rats to tetrachloroethylene at 10 and 600 ppm, respectively (Pegg et al. 1979).

Studies quantifying metabolites in urine after inhalation exposure of laboratory rodents also show dose-dependency. Following a 6-hour inhalation exposure, the amount of tetrachloroethylene excreted as metabolites decreased with increasing exposure concentration in both F344 rats and B6C3F1 mice (Reitz et al. 1996). In rats exposed to 11.9, 318, or 1,146 ppm tetrachloroethylene, 33, 14.6, and 11.3% was excreted as metabolites, respectively. In mice exposed to 11, 365, or 1,201 ppm tetrachloroethylene, 85, 44, and 26% of the dose was excreted as metabolites.

3.4.3.2 Oral Exposure

Limited data on metabolism after oral exposure are available. Swiss-Cox mice were administered tetrachloroethylene in doses of 0, 20, 100, 200, 500, 1,000, 1,500, and 2,000 mg/kg/day in corn oil by gavage for 6 weeks (Buben and O'Flaherty 1985). The amount of total metabolites found in the urine increased logarithmically with dose and approached a plateau with doses of tetrachloroethylene higher than 1,000 mg/kg/day (Buben and O'Flaherty 1985).

3.4.3.3 Dermal Exposure

3.4.4 Elimination and Excretion

Exhalation of unmetabolized parent compound is the primary route of excretion of an absorbed dose of tetrachloroethylene in humans, regardless of the route of exposure. The relative importance of excretory routes in animals depends on the concentration in air, the species, and the sex of animal. Mice excrete more tetrachloroethylene as urinary metabolites, and much less as unmetabolized parent compound in exhaled breath, than either rats or humans do. Tetrachloroethylene has a long half-life in adipose tissue because of its high adipose:blood partition coefficient and because of the relatively low rate of blood perfusion to this tissue.

3.4.4.1 Inhalation Exposure

In six male volunteers exposed by inhalation for 4 hours to either 72 or 144 ppm tetrachloroethylene, most (80–100%) of the total compound absorbed was exhaled unchanged after 162 hours (Monster et al. 1979). From concentration-time course curves of tetrachloroethylene in the exhaled air and blood of male volunteers, the half-lives of tetrachloroethylene in three major body compartments were calculated to be 12–16 hours for the vessel-rich group, 30–40 hours for the muscle group, and 55 hours for the adipose group (Monster et al. 1979). Chiu et al. (2007) exposed six male volunteers to 1 ppm tetrachloroethylene for 6 hours, and reported average recovery of tetrachloroethylene in exhaled air to be 82%. The concentration of tetrachloroethylene in alveolar air was determined for volunteers (three males, three females) exposed to 0.02–0.40 mmol/m^3 (0.5–9.8 ppm) of the chemical for durations of 1–60 seconds (Opdam and Smolders 1986). Measurements made in the postexposure period showed that tetrachloroethylene concentrations increased with residence time of the chemical in the lung for residence times ranging from 5 to 10 seconds. This could be explained by excretion of tetrachloroethylene by mixed venous blood. The study authors stated that the concentration of tetrachloroethylene in arterial blood could be reasonably estimated by the concentration of the chemical in alveolar air during normal breathing (residence time of about 5 seconds).

In humans, the urinary excretion of metabolites of tetrachloroethylene represents a small percentage of the absorbed dose of tetrachloroethylene following inhalation exposure. Urinary excretion of trichloroacetic acid represented <1% of the total estimated absorbed dose of tetrachloroethylene in volunteers exposed by inhalation to 72 or 144 ppm for 4 hours (Monster et al. 1979) or to 1 ppm for 6 hours (Chiu et al. 2007).

Volkel et al. (1998) observed dose-dependent increases in the excretion of trichloroacetic acid and N-acetyl-S(trichlorovinyl)-L-cysteine in volunteers (three males and three females) exposed for 6 hours to concentrations of 10, 20, and 40 ppm. Mean estimates of the cumulative urinary excretion of trichloroacetic acid (adjusted for body weight) were 0.07, 0.18, and 0.29 µmol/kg body weight up to 78 hours after exposure to 10, 20, and 40 ppm, respectively; estimates of cumulative excretion of N-acetyl-S(trichlorovinyl)-L-cysteine were 0.65, 2.02, and 3.01 nmol/kg body weight, respectively, up to 35 hours after exposure (Volkel et al. 1998). It has been reported that the urinary excretion of trichloroacetic acid in volunteers increased linearly with tetrachloroethylene concentrations in the air and plateaued at 50 ppm (Ikeda et al. 1972). This finding indicates that the metabolism of tetrachloroethylene is saturable and that the concentration of urinary metabolites would not reflect the amount of exposure at a concentration above the saturation of metabolism. Another study showed that 67 hours after a 3-hour exposure to tetrachloroethylene vapors, the excretion of trichloroacetic acid in the urine of four male volunteers was 1.8% of the estimated tetrachloroethylene retained (Ogata et al. 1971). Dry cleaning employees showed an increased trend of excretion of thioethers throughout the week, but the significance of this finding is unclear since the levels of thioethers were well within the range found in unexposed individuals (Lafuente and Mallol 1986). A linear relationship was found for the urinary concentration and the exposure concentration for workers exposed to tetrachloroethylene in various industries (Ghittori et al. 1987; Imbriani et al. 1988). The biological half-life of urinary metabolites of tetrachloroethylene was found to be about 6 days in occupationally exposed individuals (Ikeda and Imamura 1973).

At the same tetrachloroethylene exposure concentrations, rats excrete greater quantities of the metabolites trichloroacetic acid and NAcTCVC than humans. Volkel et al. (1998) compared the excretion of trichloroacetic acid and NAcTCVC in rats exposed to 10, 20, or 40 ppm tetrachloroethylene for 6 hours with results observed in humans (see above). Greater cumulative excretion of both metabolites was seen in rats compared with humans; cumulative 72-hour excretion of trichloroacetic acid in exposed male and female rats was 1.92, 3.44, and 6.55 µmol/kg body weight at 10, 20, and 40 ppm, respectively, while corresponding cumulative 60-hour excretion of NAcTCVC was 3.48, 7.14, and 22.98 nmol/kg body weight (Volkel et al. 1998).

Mice excrete much higher quantities of urinary tetrachloroethylene metabolites when compared with rats exposed to the same concentration and duration. In two studies, both using a 6-hour inhalation exposure to 10 ppm radiolabelled tetrachloro[1,2-14C]ethylene, male Sprague-Dawley rats exhaled 68% of the absorbed radioactivity as unmetabolized parent compound (Pegg et al. 1979), while male B6C3F1 mice

excreted only 12% through this route (Schumann et al. 1980). Exhalation of radiolabelled carbon dioxide represented 3.6% of the dose in rats, (Pegg et al. 1979) and 7.9% in mice (Schumann et al. 1980). Finally, urinary excretion of nonvolatile metabolites represented 18.7% of the absorbed radioactivity in rats and 62.5% in mice (Pegg et al. 1979; Schumann et al. 1980). In a study by Yllner (1961), female mice (unspecified strain) exposed for 2 hours to 14C-tetrachloroethylene vapors at a concentration reported to yield a dose of 1,300 mg/kg absorbed 70% of the dose. In 4 days, 90% of the absorbed radioactivity was excreted: 70% in expired air, 20% in the urine, and <0.5% in the feces. Trichloroacetic acid and oxalic acid comprised 52 and 11% of the label in the urine, respectively. Traces of dichloroacetic acid were also present in the urine. The apparent disagreement between the results of Yllner (1961) and those of Schumann et al. (1980) regarding the percentage of unchanged tetrachloroethylene in the expired air suggests that as the body burden of tetrachloroethylene increases, the percentage of unchanged parent compound excreted increases (Green 1990).

The study in rats by Pegg et al. (1979) showed dose-dependent changes in excretion pathways; at a higher exposure concentration, a larger fraction of the absorbed dose was exhaled as unmetabolized parent compound. In rats exposed to 10 ppm tetrachloroethylene, 68% of the absorbed radioactivity was exhaled as unmetabolized parent compound and 3.6% was exhaled as CO_2, while in rats exposed to 600 ppm, the proportions exhaled as unmetabolized tetrachloroethylene and CO_2 were 88 and 0.7%, respectively. The rats' 72- hour urinary excretion of nonvolatile metabolites represented 18.7% of the absorbed dose at 10 ppm and 6.0% at 600 ppm (Pegg et al. 1979).

Volkel et al. (1998) showed markedly (>3-fold) higher excretion of glutathione-dependent metabolites in male Wistar rats compared with females when both were exposed for 6 hours to a high concentration (400 ppm) of tetrachloroethylene. Cumulative excretion of NAcTCVC was 414.8 nmol/kg body weight in males, compared with 125.8 nmol/kg body weight in females. Higher levels (1.6–2-fold) of the oxidative metabolites, trichloroacetic acid and dichloroacetic acid, were also excreted by males than by females (Volkel et al. 1998).

The half-lives for elimination of trichloroacetic acid and NAcTCVC in urine have been estimated to be 45.6 and 14.1 hours, respectively, in humans and 11.0 and 7.5 hours, respectively, in rats after inhalation exposure for 6 hours to 10, 20, or 40 ppm tetrachloroethylene (Volkel et al. 1998).

3.4.4.2 Oral Exposure

The only study of the excretion of tetrachloroethylene and metabolites following oral exposure in humans is a case report of a 6-year-old boy who accidentally ingested 8–10 mL of pure tetrachloroethylene (Koppel et al. 1985). The bulk of the ingested tetrachloroethylene was exhaled unchanged; however, this was not under normal conditions since the patient was hyperventilated to facilitate pulmonary elimination of the compound. Tetrachloroethylene, trichloroacetic acid, and trichloroethanol were detected and quantified in the urine. Total urinary tetrachloroethylene decreased from 30 μg on day 1 of treatment to 3 μg on day 3. Total urinary trichloro-compounds increased from 8 mg on day 1 to 68 mg on day 3.

Male F344 rats given a daily oral dose of 1,500 mg/kg tetrachloroethylene for 42 days had evidence of kidney damage. In addition, radiolabelled material included with the doses given on days 1, 17, and 42 was detected in bile and urine (Green et al. 1990).

In animals, exhalation of unchanged tetrachloroethylene was the main route of excretion of the orally administered chemical. Sprague-Dawley rats given a single oral dose of tetrachloroethylene (1 mg/kg) excreted 72% of the absorbed dose in the breath as the unmetabolized component and 16% as metabolites in the urine over a 72-hour period (Pegg et al. 1979). When the administered dose was increased to 500 mg/kg, the percentage of the dose exhaled as unmetabolized parent compound over a 72-hour period increased to 90%, whereas the percentage of the dose excreted as metabolites in the urine dropped to 5%. Similar results were reported in Sprague-Dawley rats following ingestion of tetrachloroethylene-saturated drinking water solutions *ad libitum* for 12 hours (Frantz and Watanabe 1983). Administration of tetrachloroethylene in the drinking water provided a dose (about 8 mg/kg) that was somewhat lower than the doses of tetrachloroethylene given in gavage studies. Excretion of the absorbed dose was similar, however, for both methods of oral administration. Of the absorbed dose, 88% was exhaled as unmetabolized parent compound and 7.2% of the absorbed radioactivity was excreted in the urine over a 72-hour period. Exhalation of unmetabolized tetrachloroethylene was also the predominant mode of excretion of an orally administered tetrachloroethylene dose in B6C3F1 mice (Schumann et al. 1980). Mice given a single oral dose of tetrachloroethylene (500 mg/kg) exhaled 83% of the absorbed dose as the unmetabolized compound and 10% as metabolites in the urine over 72 hours. Exposure at 500 mg/kg resulted in saturation of oxidative metabolism in the mouse. There was a shift in the route of elimination from metabolism and urinary excretion to excretion in expired air.

A comparison of the disposition of tetrachloroethylene in Sprague-Dawley rats and Beagle dogs following oral exposure indicates that the rate and magnitude of exhalation and metabolism are markedly higher in the rat than the dog (Dallas et al. 1994a). Although exhalation of tetrachloroethylene was not measured directly, the smaller blood:air partition coefficient in rats (19.6) compared to dogs (40.5) indicates that tetrachloroethylene more readily diffuses from the pulmonary blood into the alveolar air of the rat. Whole-body clearance of tetrachloroethylene in rats and dogs treated with a single oral dose was 30.1 mL/minute/kg at 3 mg/kg and 32.5 mL/minute/kg at 10 mg/kg for rats, and 14.6 mL/minute/kg at 3 mg/kg and 25 mL/minute/kg at 10 mg/kg for dogs (Dallas et al. 1995).

Tetrachloroethylene may also be eliminated via secretion into breast milk. Tetrachloroethylene was detected in goat's milk as early as 30 minutes after intraruminal administration of a mixture containing tetrachloroethylene and two other solvents (Hamada and Tanaka 1995). Increasing concentrations were seen up to 6.5 hours after dosing, and tetrachloroethylene remained at a detectable concentration in milk 24 hours after exposure (Hamada and Tanaka 1995)

3.4.4.3 Dermal Exposure

Volunteers who immersed their thumbs for 30 minutes in liquid tetrachloroethylene exhaled the compound unchanged for time periods exceeding 5 hours (Stewart and Dodd 1964). The maximum mean alveolar air concentration of tetrachloroethylene in these subjects was 0.3 ppm, and the study authors were able to construct concentration-time curves for the mean alveolar tetrachloroethylene concentrations.

Following immersion (up to their shoulders) of anesthetized hairless guinea pigs in water containing 10–64 ppb tetrachloroethylene, about 14% of the estimated dose was excreted in the urine during the 4 weeks after exposure (Bogen et al. 1992). During the 6 days after exposure, 95% of the metabolized dose was excreted in the urine, relative to 95% of the metabolized dose excreted in the urine in 1 day following a subcutaneous injection.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various

combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in

humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

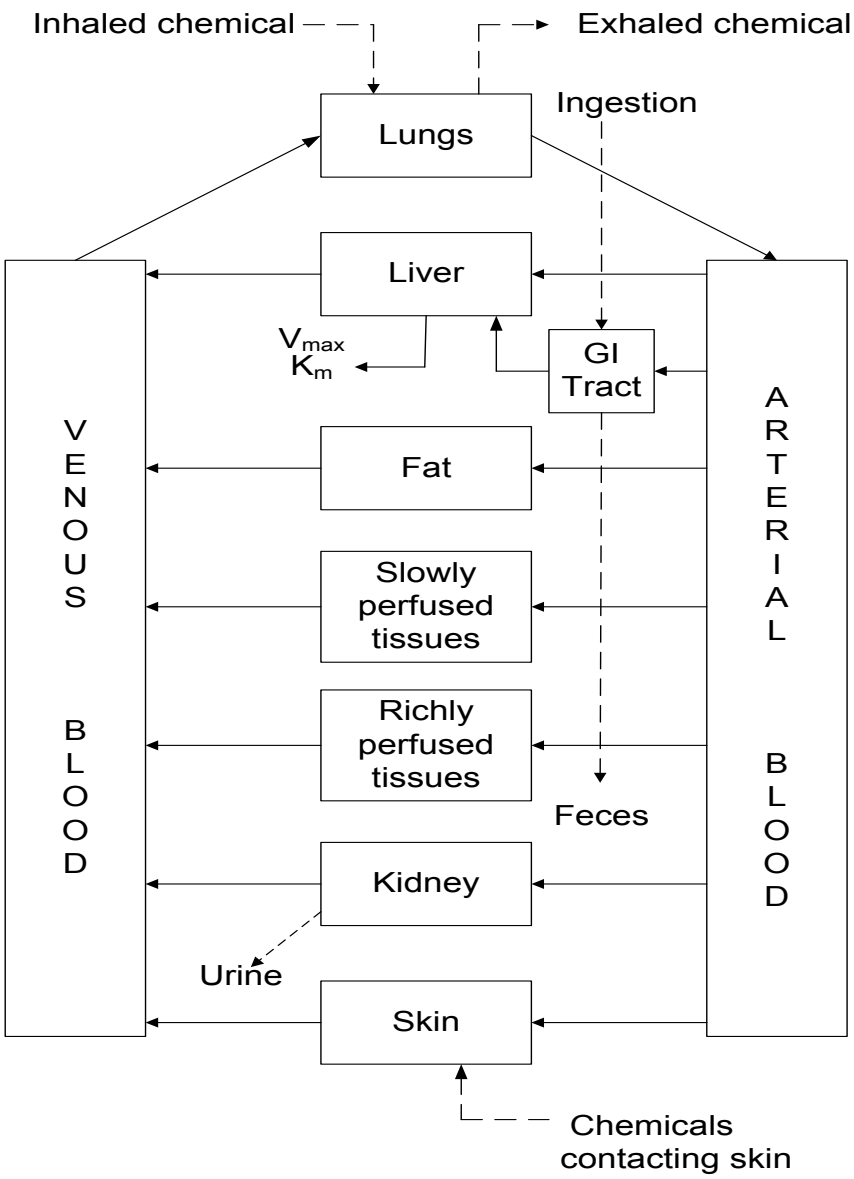
If PBPK models for tetrachloroethylene exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

A number of PBPK models have been developed over the past 25 years to predict blood or target tissue doses of tetrachloroethylene or its metabolites after inhalation, oral, or dermal exposure in animals (Bois et al. 1990; Dallas et al. 1994, 1995; Fisher et al. 1997; Hattis et al. 1990, 1993; Loizou 2001; Poet et al. 2002; Rao and Brown 1993; Reitz et al. 1996). In addition, several PBPK models have been developed and/or applied for the purpose of evaluating ethnic differences in toxicokinetics (Jang and Droz 1997), age-related differences (Clewell et al. 2004; Rodriguez et al. 2007; Sarangapani et al. 2003; Yokley and Evans 2008), or gender-related differences (Clewell et al. 2004; Sarangapani et al. 2003) in tetrachloroethylene toxicokinetics. NRC (2010), in its review of an earlier draft EPA Toxicological Review of Tetrachloroethylene, expressed concerns regarding the inadequate validation of model predictions after oral dosing and recommended that a harmonized PBPK modeling approach be used to synthesize the various models into a single structure, particularly for the purpose of route-to-route extrapolation. In response to these concerns and recommendations, Chiu and Ginsberg (2011) developed a harmonized PBPK model for oral and inhalation exposure to tetrachloroethylene in mice, rats, and humans. The model was based on the authors' previously developed model for trichloroethylene (Chiu et al. 2009). This model is discussed in further detail below. Other PBPK models are not described in detail because the Chiu and Ginsberg (2011) model was developed most recently and has the advantage of integrating the three species and two primary exposure routes of interest for risk assessment.

Chiu and Ginsberg (2011) Model

Description of the Model. The structure of the Chiu and Ginsberg (2011) model is shown in Figure 3-5 and parameters and values for rats, mice, and humans are listed in Table 3-8. This model includes eight tissue compartments: respiratory tract, gastrointestinal tract, kidney, liver, fat, rapidly perfused and slowly perfused tissues, and venous blood. Metabolism is assumed to occur in the respiratory tract, kidney, and liver. Metabolism occurring in the respiratory tract consists of tetrachloroethylene oxidation, with a fraction of oxidative flux undergoing instantaneous elimination

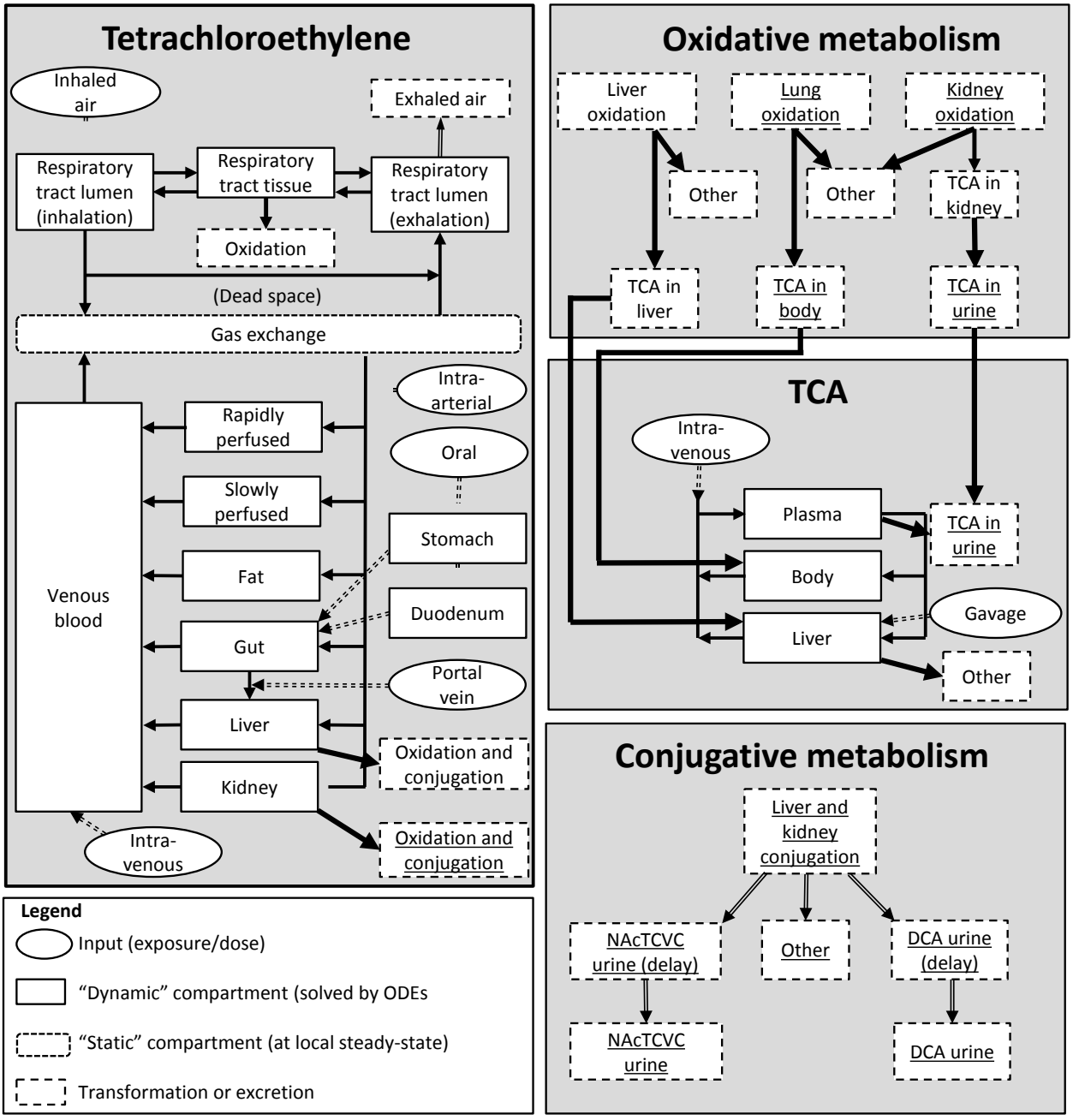
Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

Figure 3-5. Overall Structure of PBPK Model for Tetrachloroethylene and Metabolites



Boxes with underlined labels are additions or modifications of the Chiu et al. (2009) model.

DCA = dichloroacetic acid; NAcTCVC = N-acetyl trichlorovinyl cysteine; ODE = ordinary differential equation; TCA = trichloroacetic acid

Source: Chiu and Ginsberg 2011

Table 3-8. Baseline and Posterior Values of PBPK Model Parameters Selected for Optimization using MCMC

Parameter description	PBPK parameter	Baseline	Posterior mode	GSD of posterior mode across chains	Range of posterior modes across chains
Human					
Alveolar ventilation (L/hour)	QP	372	476	1.1	450–640
Hepatic oxidation (linear) (L/hour)	VMax/KM	0.353	0.454	1.08	0.346–0.468
Renal oxidation (linear) (L/hour)	VMaxKid/KM Kid	0.00076	0.0947	1.09	0.0702–0.105
Hepatic GSH conjugation (linear)	VmaxTCVG/ KMTCVG	0.0196	5.26	17.1	0.00194–5.48
Rate constant for urinary excretion of NAcTCVC (/hour)	kNAT	–	0.28	1.07	0.228–0.293
Fraction of GSH conjugation to urinary NAcTCVC	FracNATUrn	–	0.000482	15.8	0.000472–1
Fraction of GSH conjugation to urinary DCA	FracDCAUrn	–	0.00022	18.5	0.0000112–0.442
Rat					
Alveolar ventilation (L/hour)	QP	10.2	6.31	1.02	6.28–6.68
V_{MAX} for saturable hepatic oxidation (mg/hour)	V_{MAX}	0.256	0.87	1.37	0.415–1.93
K_M for saturable hepatic oxidation (mg/L)	K_M	69.7	31.1	1.39	14.8–71.9
Hepatic GSH conjugation (linear)	VmaxTCVG/ KMTCVG	2.22	0.00204	1.27	0.00131–0.00355
Rate constant for urinary excretion DCA (/hour)	kDCA	–	0.129	1.65	0.0758–0.451
Fraction of GSH conjugation to urinary NAcTCVC	FracNATUrn	–	0.0143	1.29	0.00919–0.0253
Fraction of GSH conjugation to urinary DCA	FracDCAUrn	–	0.702	1.26	0.43–0.98
Mouse					
Alveolar ventilation (L/hour)	QP	2.09	2.89	1.03	2.86–3.22
V_{MAX} for saturable oxidation (mg/hour)	V_{MAX}	0.23	0.026	1.16	0.022–0.0369
K_M for saturable oxidation (mg/L)	K_M	88.6	0.417	1.28	0.338–0.892
Linear oxidation pathway	Vmax2/KM2	–	0.0188	1.05	0.0165–0.0207
Linear conjugation pathway	VmaxTCVG/ KMTCVG	0.656	0.0000683	3.83	0.0000305–0.00179

Table 3-8. Baseline and Posterior Values of PBPK Model Parameters Selected for Optimization using MCMC

Parameter description	PBPK parameter	Baseline	Posterior mode	GSD of posterior mode across chains	Range of posterior modes across chains
Rate constant for TCA plasma→urine (/hour)	kUrnTCA	1.48	0.638	1.05	0.56–0.695
Rate constant for hepatic TCA→other (/hour)	kMetTCA	2.93	1.26	1.05	1.11–1.38

DCA = dichloroacetic acid; GSD = geometric standard deviation; GSH = glutathione; MCMC = Markov Chain Monte Carlo; NAcTCVC = N-acetyl trichlorovinyl cysteine; PBPK = physiologically based pharmacokinetic; TCA = trichloroacetic acid; TCVG = *S*-(1,2,2-trichlorovinyl)glutathione

Source: Chiu and Ginsberg 2011

within the respiratory tract or translocation to the body. In both liver and kidney, a fraction of the tetrachloroethylene is converted to the GSH conjugate, *S*-(1,2,2-trichlorovinyl)glutathione; disposition of this metabolite is simulated with a simplified structure allowing for urinary excretion of the downstream metabolites NAcTCVC or dichloroacetic acid or an alternative fate that encompasses all other possible fates, such as activation by beta-lyase to products other than dichloroacetic acid or activation to reactive products by flavin-containing monooxygenases or sulfoxidation. Urinary excretion of NAcTCVC and dichloroacetic acid is modeled using a fitted delay parameter to better simulate available time-course data. The total rate of oxidation of tetrachloroethylene in liver, kidney, and lung is split into fractions leading to trichloroacetic acid and to other oxidative pathways. A second, saturable oxidative pathway was added to the liver to account for evidence of tetrachloroethylene metabolism by CYPs other than CYP2E1. A fraction of the trichloroacetic acid formed in the kidney is assumed to be excreted in the urine, with the remainder translocated to the body compartment.

Oxidative metabolism in the liver and kidney of humans is modeled as a linear process due to a lack of data on the degree of saturation. Oxidative metabolism in the rat and mouse is modeled as a saturable process, with an additional linear process in the mouse to provide better fit than seen with a single saturable process. Glutathione conjugation is modeled as a linear process in all three species.

Baseline Parameter Values. The Chiu and Ginsberg (2011) model used baseline physiological values primarily obtained from standard references including the International Commission on Radiological Protection (ICRP 2002) and Brown et al. (1997). Partition coefficients were obtained by pooling available *in vitro* data from six studies (Gargas et al. 1989; Gearhart et al. 1993; Koizumi 1989; Mahle et al. 2007; Mattie et al. 1994; Reitz et al. 1996). In addition, *in vitro* metabolic parameters from the published literature were selected and converted to Vmax, Km, and/or Vmax/Km values using the microsomal and cytosolic protein content and tissue-specific cellularity for liver and kidney in mice, rats, and humans.

Parameter Optimization. Model predictions obtained with the selected baseline values were compared with *in vivo* inhalation data, and the results were used to select parameters for optimization. All of the tetrachloroethylene metabolism parameters were selected for optimization, while most physiological parameters (with the exception of alveolar ventilation rate) and partition coefficients were held at their baseline values. The selected parameters were optimized using a limited Bayesian approach with flat priors and inferences obtained by Markov Chain Monte Carlo (MCMC). Table 3-8 shows the baseline parameter values and posterior mode values obtained using MCMC.

Model Evaluation. Model predictions were compared with tissue, blood, and urinary levels of tetrachloroethylene and its metabolites from *in vivo* studies of mice, rats, and humans. Residual errors within a factor of 2–3 were observed for most of the data. The poorest predictions in mice were the fraction of tetrachloroethylene exhaled and the liver concentration of trichloroacetic acid; in rats, the concentration of tetrachloroethylene in fat had the highest residual error. The evaluation dataset for humans did not contain enough data to evaluate the uncertainty in the internal dose metrics.

Target Tissues. The model was used to predict a variety of dose metrics including: area under the tetrachloroethylene blood concentration-time curve (mg h/L/day), fraction of dose oxidized, fraction of dose conjugated, and systemic trichloroacetic acid dose (mg/kg/day). The metric with the lowest uncertainty across all three species was the blood concentration metric. The fraction conjugated was most uncertain, especially in humans, with a 3,000-fold range across chains in the human model.

Species Extrapolation. The model simulates toxicokinetics in mice, rats, and humans. Models for these species were developed by optimization of metabolic parameters using a limited Bayesian analysis. The scaled rat and human models have been evaluated against independent observations not used to estimate model parameter values (Chiu and Ginsberg 2011).

Mass balance inferences based on the estimates of various dose metrics in the Chiu and Ginsberg (2011) model confirm the species differences in metabolism. In mice exposed by inhalation, the model predicts that ~20% of the intake is metabolized, of which only ~1% is conjugated via GSH and the balance oxidized. In mice exposed orally, ~60% of the intake is metabolized, of which only ~2% is conjugated and the balance oxidized. In rats exposed by inhalation, ~4% of the intake is metabolized, of which ≤0.3% is conjugated and the balance oxidized. In rats exposed orally, ~10% of the intake is metabolized, of which ≤0.6% is conjugated and the balance oxidized. In humans exposed by inhalation, ~10% of the intake is metabolized; after oral exposure, ~20% of the intake is metabolized. The fractions of metabolism attributable to the oxidative and conjugative pathways in humans were very uncertain, with GSH conjugation estimates ranging from <0.003 to 10% after inhalation and from 0.006 to 19% after oral exposure (the high values assume that all metabolism occurred via this pathway).

Interroute Extrapolation. The tetrachloroethylene model (Chiu and Ginsberg 2011) simulates tetrachloroethylene kinetics associated with inhalation, oral, and intravenous dosing. The model predicted very similar blood concentration-time AUC estimates for oral and inhalation exposures in

humans (~2 mg hour/L/day per mg/kg/day oral dose or ppm air across a wide range of doses and exposure concentrations). Model predictions of AUC in rats were about 2-fold higher after inhalation exposure than after oral exposure, presumably due to higher hepatic metabolism after oral exposure. In mice, the route differences were marked; oral exposure resulted in AUC estimates about 5% of the AUC estimates after inhalation exposures, again due to the higher hepatic metabolism.

Risk Assessment. EPA (2012a) used the human model to extrapolate from an inhalation reference concentration to an oral reference dose. The basis of the inhalation reference concentration was epidemiological evidence of neurotoxicity (neurobehavioral impairments and decrements in color vision) in humans exposed to tetrachloroethylene. The interroute extrapolation was based on the AUC of blood tetrachloroethylene as the internal dose metric; this metric was presumed to be a step in the neurotoxicity pathway. Simulations by Chiu and Ginsberg (2011) indicated that route-to-route dose conversions are not very sensitive to the choice of dose metric; other metrics yielded route-to-route conversions within 1.4-fold of the conversion resulting from blood AUC.

EPA (2012a) also used the Chiu and Ginsberg (2011) model for interspecies extrapolations in the cancer risk assessment. For extrapolation from mice to humans in the assessment of liver tumors, the total rate of oxidative metabolism was used as the dose metric; AUC for trichloroacetic acid in the liver was also evaluated for comparison purposes. For mononuclear cell leukemia in rats, the AUC of the parent compound in blood was used as a dose metric, as the proximate toxicant for this neoplasm is not known. Parent compound AUC in blood was also selected as the internal dose metric for renal tumors in rats; this metric was chosen in light of the substantial uncertainty in model predictions for GSH conjugation in humans.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

The absorption, distribution, storage, and excretion of tetrachloroethylene are largely determined by its lipophilic nature. The blood:air partition coefficient estimated for humans is 10–20, the fat:air partition coefficient is 1,450–1,638, and the fat:blood partition coefficient is 125–159 (Byczkowski and Fisher 1994; Gearhart et al. 1993; Ward et al. 1988). Therefore, tetrachloroethylene is readily taken up by blood and is then distributed to fatty tissues where it is retained with a half-life of about 55 hours. The affinity of tetrachloroethylene for fat also results in its translocation into milk (Byczkowski and Fisher 1994).

The lipophilicity of this compound may also lead to diminished absorption of tetrachloroethylene administered orally in an oil vehicle compared with water-soluble vehicles.

Effect of Dose and Duration of Exposure on Toxicity. Available data show saturation of the oxidative metabolic pathways for tetrachloroethylene in rats and mice (Pegg et al. 1979; Reitz et al. 1996), with limited evidence for saturation in humans exposed to high airborne concentrations (Ohtsuki et al. 1983; Seiji et al. 1989). In contrast, there is no evidence for saturation of metabolism via glutathione conjugation, which represents a relatively small fraction of the metabolic fate of tetrachloroethylene administered either orally or via inhalation, in the available data. However, there is a great deal of uncertainty in the degree of glutathione conjugation versus oxidative metabolism of tetrachloroethylene in humans (Chiu and Ginsberg 2011), and it is possible that high exposures may lead to nonlinearities in the production and elimination of downstream metabolites of this pathway.

Route Dependent Toxicity. In humans, exposure route has only a small impact on the pharmacokinetic fate of tetrachloroethylene. PBPK simulations have suggested that the total metabolism of tetrachloroethylene is about twice as high after oral exposure of humans compared with inhalation exposure (Chiu and Ginsberg 2011); regardless of route, ≥80% of tetrachloroethylene is not metabolized. In rats, the route differences in metabolism are similar to those in humans (Chiu and Ginsberg 2011). In mice, however, oral exposure results in oxidative metabolism of about 60% of the administered dose, while only 20% is metabolized after inhalation (Chiu and Ginsberg 2011). The differences in total, oxidative, and conjugative metabolism are important predictors of target organ and toxicity because the parent compound, oxidative metabolites, and glutathione metabolites are believed to be (or be converted to) the proximate toxicants associated with neurotoxicity, hepatotoxicity and liver tumors, and renal toxicity and tumors, respectively (Bale et al. 2005; Benane 1996; Briving et al. 1986; Green 1990; Kyrklund et al. 1984, 1990; Lash and Parker 2001; Lash et al. 1998, 2002, 2007; Shafer et al. 2005), as discussed below.

3.5.2 Mechanisms of Toxicity

Based on effects reported in humans and in animal studies, the primary targets for tetrachloroethylene toxicity are the nervous system, kidney, and liver; the immune system may also be affected, although data on this end point are limited.

Neurological Effects. Experimental studies in rodents have shown that tetrachloroethylene alters the fatty acid pattern of brain phospholipids and amino acids (Briving et al. 1986; Kyrklund et al. 1984, 1987, 1988, 1990), which could be partially responsible for tetrachloroethylene-induced neurotoxic effects. Alternatively, the effects of tetrachloroethylene on the central nervous system may result from the incorporation of this lipophilic compound into brain membranes, which may alter neural conduction velocity. A study by Wang et al. (1993), which examined neuronal and glial cell markers in different regions of the brain in rats exposed to tetrachloroethylene, suggests that the frontal cerebral cortex is more sensitive to tetrachloroethylene than other regions of the brain and that cytoskeletal elements are more sensitive than cytosolic proteins.

Other studies have shown that tetrachloroethylene can interfere with voltage-gated channels and neuronal receptors. Shafer et al. (2005) demonstrated that tetrachloroethylene perturbs whole-cell calcium currents in nerve growth factor-differentiated pheochromocytoma (P12) cells. An *in vitro* study found that Xenopus oocytes exposed to tetrachloroethylene at 0.065 mM showed marked inhibition (40–62%) of human and rat neuronal nicotinic acetylcholine receptors (Bale et al. 2005). Related compounds, including trichloroethylene, exhibit effects on a wide range of inhibitory and excitatory receptors and ion channels (reviewed by Bale et al. 2011). Additional data regarding the mechanisms by which tetrachloroethylene produces changes in the central nervous system are needed.

Hepatic Effects. In contrast to nervous system effects, which are thought to be a result of tetrachloroethylene itself, effects on the liver, including cancer in mice, are thought to be a result of metabolism to oxidative metabolites, including trichloroacetic acid and dichloroacetic acid (Benane et al. 1996). Rodents, especially mice, produce more trichloroacetic acid than humans (Hattis et al. 1990). In addition, the trichloroacetic acid appears to be preferentially localized in the liver after oral exposure; Green et al. (2001) showed that gavage administration of tetrachloroethylene in mice resulted in the formation of trichloroacylated protein adducts in the liver, primarily in the centrilobular zones, and not in other organs.

Hepatic peroxisome proliferation induced in mice by trichloroacetic acid may play a role in the liver carcinogenicity of tetrachloroethylene in this species. A study by Maloney and Waxman (1999) showed that trichloroacetic acid and dichloroacetic acid, but not the parent tetrachloroethylene compound, activated mouse and human peroxisome proliferator-activated receptor (PPAR) receptor α (highly expressed in the liver of rodents; less highly expressed in the human liver) expressed in COS-1 cells. The

role of peroxisome proliferation in hepatocarcinogenicity appears may involve induction of peroxisomal enzymes that produce hydrogen peroxide as a byproduct without inducing catalase. In addition, peroxisome proliferators may promote endogenous lesions by sustained DNA synthesis and hyperplasia, which may be sufficient for tumor formation (Bentley et al. 1993).

Some data indicate that exposure to tetrachloroethylene itself (at concentrations approximating the blood levels attained by exposed human subjects, 1.5 μg/mL) induces toxicity (measured as the release of AST and LDH and reduction in mitochondrial reducing activity) and lipid peroxidation (measured as thiobarbituric acid reactive substances production) in rat hepatocytes exposed *in vitro* (Costa et al. 2004). Increased cytotoxicity (MTT assay) was also observed in isolated rat hepatocytes treated with tetrachloroethylene in the range of 3 to 49 mM (Zapór et al. 2002). The increased production of hydrogen peroxide may increase DNA damage.

An *in vitro* study suggests that tetrachloroethylene can directly affect hepatocytes. Vapor exposure of rat hepatocytes to tetrachloroethylene (2–4 μL) significantly decreased the hepatocyte uptake of taurocholate, ouabain, and 2-aminoisobutyric acid, all substances that require adenosine 5'-triphosphate (ATP) for uptake (Kukongviriyapan et al. 1990). The uptake of cadmium and 3-*O*-methyl-D-glucose, substances that do not require ATP, was not affected. Cellular ATP was decreased by tetrachloroethylene, but only at cytotoxic levels. Tetrachloroethylene also decreased membrane ATPase activity, leading the investigators (Kukongviriyapan et al. 1990) to hypothesize that the effect of tetrachloroethylene on transport may result from both a decrease in ATP levels and an inhibition of cell membrane ATPases. Another *in vitro* study (Benane et al. 1996) showed that tetrachloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, effectively inhibited gap junction intercellular communication in rat hepatocytes; this reduction in intercellular communication is thought to play an important role in tumor promotion.

Although P-450 metabolism is critical for tetrachloroethylene-induced liver toxicity, the relative contribution of GSH conjugation to effects in this target organ has not been fully elucidated. In a study conducted using isolated rat liver cells, Lash et al. (2007) showed that cytotoxicity was not dependent on P-450 metabolism alone, since significant toxicity was observed despite perturbations to the P-450 pathway. Although *S*-(1,2,2-trichlorovinyl)glutathione generated in the liver is thought to be transported to the kidneys, alterations in the GSH status of liver cells influence toxicity induced by tetrachloroethylene. Decreased cellular GSH enhanced, while increased cellular GSH diminished,

tetrachloroethylene-induced cytotoxicity in hepatocytes (Lash et al. 2007), suggesting that interactions between these metabolic pathways likely contribute to liver toxicity.

Renal Effects. A low incidence of kidney cancer has been observed in male rats following inhalation exposure to tetrachloroethylene (NTP 1986). Kidney cancer may in part be a result of the formation of the genotoxic metabolites from *S*-(1,2,2-trichlorovinyl)glutathione catalyzed by β-lyase, CYP3A, or flavin-containing oxygenases, or from cellular damage and regeneration associated with lipid peroxidation from glutathione depletion. In agreement, the increased susceptibility of male rats to renal tumors correlates with increased *S*-(1,2,2-trichlorovinyl)glutathione formation in male rats relative to female rats (Lash et al. 1998). Treatment of renal cells with tetrachloroethylene or *S*-(1,2,2-trichlorovinyl)glutathione *in vitro* at up to 10 mM induced cytotoxicity, as measured by increased leakage of LDH from cells and/or compromised respiratory function of mitochondria (inhibition of state 3 respiration) (Lash et al. 2002, 2007). In addition, NAcTCVC and N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine sulfoxide (at 0.1 mM) were shown to be cytotoxic to rat renal epithelial cells, with the sulfoxide conjugate being more toxic than its mercapturic acid (Werner et al. 1996). Taken together, these data suggest that GSH conjugation of tetrachloroethylene likely plays a significant role in tetrachloroethylene-induced renal toxicity. In contrast, modulation of P-450 activity (using specific or nonselective inhibitors or inducers) had no significant effect on tetrachloroethylene-induced kidney toxicity (Lash et al. 2007).

Tetrachloroethylene has also been shown to selectively affect the tubular S2 segment in the kidney of male rats through the accumulation of α-2μ-globulin (Bergamaschi et al. 1992). This mechanism of renal effects observed in male rats may not be relevant to human risk assessment because humans do not produce α-2μ-globulin or proteins in the same family (lipocalin) in large quantities as observed in male rats (Swenberg et al. 1989). However, the histopathology findings in male rats in the two inhalation bioassays of tetrachloroethylene (NTP 1986; JISA 1993) were not consistent with α-2μ-globulin nephropathy (NRC 2010). In addition, similar renal effects were observed in female rats and both sexes of mice (JISA 1993; NRC 1986), providing additional evidence against α-2μ-globulin-mediated effects. Taken in conjunction with evidence for injury associated with glutathione metabolites of tetrachloroethylene, the available information indicates that accumulation of α-2μ-globulin is not the primary mechanism of renal toxicity and carcinogenicity associated with tetrachloroethylene exposure.

Immune Effects. Data from Seo et al. (2008b) showed that exposure to tetrachloroethylene (at 0.1–1 mg/L) increased histamine release in rat peritoneal mast (NPMC) and basophilic leukemia (RBL-2H3) cells. Treatment with tetrachloroethylene also increased mRNA expression of IL-4 ($p<0.05$) and TNF-α

($p>0.05$) as well as the production of these mediators ($p<0.05$ for both) in RBL-2H3 cells. A dose-dependent increase in antigen-induced histamine release from mouse bone marrow cells treated with tetrachloroethylene was reported in another study from this laboratory (Seo et al. 2012). These data suggest possible mechanisms for tetrachloroethylene-induced perturbation of the immune response to allergens, and exacerbation of inflammation. An *in vitro* study by Kido et al. (2013) also showed effects on pro-inflammatory cytokine gene expression. Significant ($p<0.05$) increases in the expression of IL-6 and IL-10 mRNA were observed in murine macrophage cells exposed to 800 µg/mL tetrachloroethylene. However, cell viability was significantly diminished at this concentration, and exposure to a higher concentration (1,000 µg/mL) yielded mRNA levels comparable to controls, so a clear dose-response relationship was not demonstrated.

3.5.3 Animal-to-Human Extrapolations

The difference in the toxic action of tetrachloroethylene in rats and mice correlates well with differences in the metabolism of the compound. Mice, which are more sensitive to the liver effects of tetrachloroethylene than rats, produce more trichloroacetic acid. Production of trichloroacetic acid in mice may result in peroxisome proliferation, a response to chemical exposure that is minimal in humans (Bentley et al. 1993). Therefore, for liver effects, the mouse may not be the most appropriate model for humans.

Although rats produce lower amounts of the intermediate *S*-(1,2,2-trichlorovinyl)glutathione in either kidney or liver cytosol or microsomes tested *in vitro* (Lash and Parker 2001), this species appears to have greater potential than mice for producing reactive intermediates in the kidney from the glutathione conjugate of tetrachloroethylene through the activity of kidney β-lyase (Green et al. 1990). The increased production of reactive metabolites may explain the higher sensitivity of rats to renal effects when compared with mice. Male rats also develop α-2µ-globulin nephropathy following exposure to tetrachloroethylene. Due to the potential contribution of α-2µ-globulin nephropathy in the observed kidney effects, the male rat is a relatively poor model for humans.

Nervous system effects have been well documented in humans. Although tetrachloroethylene is thought to be responsible for the nervous system effects, the possible role of metabolites has not been well studied. If tetrachloroethylene is the active nervous system toxicant, metabolism to trichloroacetic acid may serve to reduce nervous system toxicity. Therefore, rats, which metabolize less tetrachloroethylene

to trichloroacetic acid than mice (Hattis et al. 1990), may serve as a better model of nervous system effects in humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to tetrachloroethylene.

No *in vitro* studies were located regarding endocrine disruption of tetrachloroethylene.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The fetus/infant has an immature (developing) blood-brain barrier that past literature has often described as being leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the blood-brain barrier, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or do they render it more vulnerable to toxic injury. Each case of chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Studies in mice suggest that tetrachloroethylene can cross the placenta and that trichloroacetic acid concentrates in the fetus (Ghantous et al. 1986). Unmetabolized tetrachloroethylene has been excreted in breast milk and was detected in an exposed infant with liver damage (Bagnell and Ellenberger 1977). Intake from tetrachloroethylene-contaminated water is expected to be greater in children than adults because children tend to drink more water on a per-kg body weight basis than adults, but this has not been experimentally determined. Absorption of tetrachloroethylene following exposure appears to be similar in adults and children, as *in vitro* blood:gas partition coefficients obtained by Mahle et al. (2004) suggest no age-related difference in partitioning between pediatric and adult blood. In support, PBPK modeling does not predict age-dependent variations in steady-state blood concentrations (Sarangapani et al. 2003). However, PBPK modeling predicts that metabolite blood concentration increases with age, associated with a concomitant increase in hepatic enzyme activity with age, indicating lower ability to metabolize tetrachloroethylene during early life stages (Clewell et al. 2004; Sarangapani et al. 2003). As the parent compound may mediate neurotoxic effects of exposure (see Section 3.5.2. Mechanisms of Toxicity), this decrease in metabolic capacity may confer increased risk to the developing nervous system. However, *in vitro* organ:air partition coefficients indicate lower fat:air, muscle:air, and brain:air coefficients in pups compared with adult rats, suggesting decreased distribution of tetrachloroethylene in the young (Mahle et al. 2004).

The data available for assessing the potential susceptibility of infants and children to the toxic effects of tetrachloroethylene are very limited. Results of some epidemiological studies indicate that exposure to tetrachloroethylene in the drinking water, ambient air, or workplace environments *in utero* or during early childhood may be associated with developmental effects such as increased rates of spontaneous abortion (Ahlborg 1990; Bosco et al. 1986; Doyle et al. 1997; Hemminki et al. 1980; Kyyrönen et al. 1989; Lindbohm et al. 1990; Windham 1991), ocular and auditory defects and other central nervous system abnormalities (Lagakos et al. 1986), oral cleft defects (Aschengrau et al. 2009; Bove et al. 1995), neural tube defects (Aschengrau et al. 2009), cardiac defects (Forand et al. 2012), impaired immunity (Lagakos et al. 1986), and increased risk of mental illness as adults (Aschengrau et al. 2012; Perrin et al. 2007). However, the data supporting a cause-and-effect relationship for these effects are inadequate. Results of some animal studies indicate that tetrachloroethylene can cause reduced fetal weight and increased skeletal and soft-tissue anomalies (Carney et al. 2006; Schwetz et al. 1975; Szakmáry et al. 1997; Tepe et al. 1980), decreased litter size (Narotsky and Kavlock 1995), neurobehavioral changes (Nelson et al.

1980; Fredriksson et al. 1993), neurochemical changes (Nelson et al. 1980), and brain composition alterations (Kyrklund and Haglid 1991).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for tetrachloroethylene from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to tetrachloroethylene are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by tetrachloroethylene are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Tetrachloroethylene

Biological monitoring for exposure to tetrachloroethylene is possible by measuring levels of the parent compound in the blood, urine, or exhaled air or trichloroacetic acid in the blood or urine. Biological monitoring for tetrachloroethylene exposure has been performed to measure both exposure occurring in the workplace and the environmental exposure of individuals at places other than the work site. In these instances, it has been demonstrated that measurement of tetrachloroethylene in exhaled air is a fairly simple, effective, and noninvasive method for assessing both occupational and nonoccupational exposure (Stewart and Dodd 1964; Stewart et al. 1961b, 1970, 1981). Tetrachloroethylene is excreted in the breath for long periods after exposure and is measurable on Monday morning following exposure the previous week (Monster et al. 1983). In an experimental exposure study, Stewart et al. (1981) found that breath concentrations reached equilibrium with exposure concentrations on the third day of each week. Based on breath analysis decay curves, Stewart et al. (1981) concluded that 16.5 hours after a male worker has been exposed to tetrachloroethylene in air at 100 ppm for 7.5 hours, his breath level should not exceed 10 ppm, while breath concentrations of a female worker should not exceed 6 ppm. Following 3 hours of exposure at 100 ppm, breath levels at 21 hours postexposure should not exceed 5 and 1 ppm for males and females, respectively.

In the experimental exposure studies of Stewart et al. (1961b, 1970, 1981), analysis of the expired breath of exposed subjects for tetrachloroethylene proved to be superior to both blood and urine analyses for determining the magnitude of the previous vapor exposure. A series of Breath Decay Curves was constructed following vapor exposures to 20, 50, 100, 150, and 200 ppm for 1, 3, and 7.5 hours, repeated for 5 days each, which permitted the estimation of the magnitude of the previous exposure. Utilizing the 30-second breath-holding technique to collect breath samples, these Breath Decay Curves provide an efficient method for determining whether overexposure has occurred (Stewart et al. 1961a, 1981).

The concentration of tetrachloroethylene in exhaled air was used to measure environmental exposure in a group of 54 healthy volunteers from an urban population (Krotoszynski et al. 1979). In this group of subjects, it was determined that 30.2% had traces of tetrachloroethylene in their breath, with a mean concentration of 2.6 ng/m^3. The measurement of tetrachloroethylene in exhaled air showed that 93% of a sample of about 300 nonoccupationally exposed residents of Bayonne and Elizabeth, New Jersey, had measurable concentrations of tetrachloroethylene in their breath (Wallace 1986). The mean concentration of tetrachloroethylene in the breath in this study was 13.3 μg/m^3, and this mean concentration was increased to 22 μg/m^3 for persons who had visited a dry cleaning establishment. Measurements of tetrachloroethylene in exhaled air were used to determine exposure in children attending a school near a factory and in occupants of a senior citizens home located near a former chemical waste dump. A control group of children had a mean tetrachloroethylene level in their exhaled air of 2.8 μg/m^3, whereas exposed children had a mean tetrachloroethylene level of 24 μg/m^3. In the senior citizens group, people living on the first floor of the home had a mean tetrachloroethylene level of 7.8 μg/m^3, whereas people living on the second floor and above had a mean tetrachloroethylene level of 1.8 μg/m^3. It was concluded that biological monitoring of tetrachloroethylene in exhaled air was an effective method of assessing total ambient tetrachloroethylene exposure in both the young and the aged (Monster and Smolders 1984).

Biological monitoring for recent, as opposed to more remote, exposure to tetrachloroethylene has also been performed by measuring concentrations of tetrachloroethylene and its principal metabolite, trichloroacetic acid, in blood and urine. However, trichloroacetic acid is not specific for tetrachloroethylene because it is also produced from the metabolism of trichloroethylene and 1,1,1-trichloroethane (Monster 1988). In a study of occupationally exposed individuals, measurements of tetrachloroethylene and trichloroacetic acid in the blood 15–30 minutes after the end of the workday at the end of the week were judged to be the best parameters for estimating exposure to the chemical. The best noninvasive method for determining tetrachloroethylene exposure was to measure the concentration of the parent compound in exhaled air. After exposure to a TWA concentration of 50 ppm of tetrachloro-ethylene, the estimated concentrations of tetrachloroethylene and trichloroacetic acid in blood were 2.2 and 5.4 mg/L, respectively; the concentration of tetrachloroethylene in exhaled air was estimated to be 22.5 ppm (Monster et al. 1983). In another study of workers exposed to tetrachloroethylene, urinary metabolites were related to vapor concentrations up to 50 ppm, but little additional increase occurred at higher concentrations (Ikeda et al. 1972). The ACGIH biological exposure index (BEI) associated with a TWA concentration of 25 ppm tetrachloroethylene is 0.5 mg tetrachloroethylene/L in blood and 3 ppm in end-exhaled air (ACGIH 2012). Jang et al. (1997) observed differences in tetrachloroethylene

metabolism between persons of Caucasian and Asian descent in a controlled human exposure study, with higher levels of tetrachloroethylene measured in exhaled breath of Caucasians.

3.8.2 Biomarkers Used to Characterize Effects Caused by Tetrachloroethylene

Hepatocellular damage and icterus have been related to exposure to tetrachloroethylene. Biomarkers of hepatic cell death, which are not specific for tetrachloroethylene, are increases in serum levels of intracellular liver enzymes including SGOT, SGPT, and LDH. Biomarkers of icterus include increased serum levels of bilirubin and alkaline phosphatase and increased urobilinogen in urine (Bagnell and Ellenberger 1977; Coler and Rossmiller 1953; Hake and Stewart 1977; Meckler and Phelps 1966; Stewart 1969). Electrophoresis of serum GGT enzymes from tetrachloroethylene-exposed workers with no other evidence of liver effects (SGOT, SGPT, serum alkaline phosphatase, LDH, and 5'-nucleotidase) has shown increases in GGT-2 and the appearance of GGT-4, which was not present in the serum of the unexposed controls (Gennari et al. 1992). The investigators indicate that further research is required to determine if changes in GGT enzymes are useful for detecting early liver changes induced by tetrachloroethylene. As increases in GGT also occur with fatty livers, pancreatitis, and following exposure to other xenobiotics (Suber 1989), this liver effect is not specific for tetrachloroethylene. Parenchymal changes detected by ultrasound may also be a useful noninvasive marker of liver effects (Brodkin et al. 1995), although it also is not specific for tetrachloroethylene.

Biomarkers of renal damage are not specific for solvents. For clinical renal damage, these include increased BUN and serum creatinine and abnormal urinalysis findings. Increased urinary levels of lysozyme and the lysosomal enzyme, *N*-acetyl-beta-D-glucuronidase, albuminuria, and other urinary markers suggesting increased shedding of epithelial membrane components from tubular cells may indicate subclinical renal damage in workers exposed to a potentially nephrotoxic chemical (Franchini et al. 1983; Meyer et al. 1984; Mutti et al. 1992; Viau et al. 1987). Voss et al. (2005) evaluated the available data supporting a variety of potential biomarkers for early detection of renal damage from solvents. Data were sufficient for evaluation of only three: urinary albumin, β2-microglobulin, and NAG. The authors concluded that, because increased albumin excretion was frequently seen in exposed workers, this parameter might be suitable for biomonitoring for renal effects. However, the authors noted the uncertainties stemming from their simplistic analysis, which did not take into account variations in exposure intensity and duration. In addition, the authors cautioned that factors associated with albuminuria, including strenuous exercise prior to sampling, as well as diabetic nephropathy and hypertension, need to be considered in the interpretation of urinary albumin levels (Voss et al. 2005).

Neurotoxic effects manifested in the central nervous system have been associated with acute and chronic exposure of humans to tetrachloroethylene. These effects may be monitored by evaluation of symptoms, neurological examination, and neuropsychological testing (Gregersen et al. 1984). Neurological effects are not specific for tetrachloroethylene. Therefore, other causes of neurological disease must be ruled out before effects are attributed to tetrachloroethylene exposure.

3.9 INTERACTIONS WITH OTHER CHEMICALS

The potential interactions between tetrachloroethylene and other chlorinated solvents are discussed in detail by ATSDR (Agency for Toxic Substances and Disease Registry 2004). As concluded by ATSDR (Agency for Toxic Substances and Disease Registry 2004), there are no studies available that directly characterize health hazards and dose-response relationships for exposures to mixtures of chlorinated solvents with tetrachloroethylene. The limited available data indicate no evidence for greater-than-additive joint toxic actions on the liver and kidney; there is some evidence that tetrachloroethylene may inhibit the effect of trichloroethylene on the liver and kidney (Goldsworthy and Popp 1987; Seiji et al. 1989). Potential interactions between tetrachloroethylene and other common indoor air contaminants (carbon monoxide, formaldehyde, methylene chloride, and nitrogen dioxide) are discussed by ATSDR (Agency for Toxic Substances and Disease Registry 2007b). While several of these compounds exert toxic effects on the same target sites, there are no data to evaluate potential interactions among them.

The hepatic monooxygenase system is primarily responsible for oxidation of tetrachloroethylene. Thus, compounds that stimulate or induce tetrachloroethylene metabolism could influence the toxicity associated with exposure to this chemical. Results of experiments that have investigated possible enhancement of tetrachloroethylene-induced toxicity by increasing tetrachloroethylene metabolism have been equivocal. Pretreatment of rats with ethanol (Cornish and Adefuin 1966; Klaassen and Plaa 1966) and phenobarbital (Cornish et al. 1973; Moslen et al. 1977) failed to enhance tetrachloroethylene hepatic toxicity. Pretreatment with polychlorinated biphenyls (PCBs), on the other hand, increased urinary excretion of tetrachloroethylene metabolites in rats and enhanced tetrachloroethylene-induced hepatotoxicity (Moslen et al. 1977).

A study was conducted to evaluate the potential interaction between tetrachloroethylene and ethanol, or tetrachloroethylene and diazepam (Stewart et al. 1977). Twelve healthy volunteers of each sex were exposed to 0, 25, or 100 ppm tetrachloroethylene vapor alone or in combination with either ethanol (0.0,

0.75, or 1.5 mL vodka/kg body weight) or diazepam (0, 6, or 10 mg/day). The subjects exhibited a decrement in performance of at least one of the behavioral or neurological tests while on either drug alone at the highest dose level, but no interaction with tetrachloroethylene resulting in additional test performance decrement could be demonstrated for either combination of solvent vapor and drug.

Giovannini et al. (1992) examined the interaction of ethanol and tetrachloroethylene on the hepatic toxicity in rats. Rats were exposed to 15% ethanol in the drinking water and/or to tetrachloroethylene aerosol for 10 minutes/day for 4 weeks. The tetrachloroethylene concentration used was not provided, but can be assumed to be very high because the rats were unconscious by the end of the 10-minute exposure period. Liver effects, necrotic foci, steatosis, and lymphocyte infiltration were worse after ethanol exposure compared to tetrachloroethylene exposure alone. When the rats were treated with both compounds, tetrachloroethylene tended to reduce the hepatic effects of ethanol. Giovannini et al. (1992) suggest that the reduction of ethanol hepatic effects by tetrachloroethylene is a result of a metabolic interaction between ethanol and tetrachloroethylene.

In a study of dry cleaning workers in China, urinary metabolite levels (total trichloro compounds) were reduced when workers were exposed to mixtures of tetrachloroethylene and trichloroethylene, as opposed to trichloroethylene alone (Seiji et al. 1989). The effect on the trichloroethylene metabolite, trichloroethanol, was greatest, with little effect on trichloroacetic acid, a metabolite of both trichloroethylene and tetrachloroethylene. The study authors indicated that because of the smaller amount of tetrachloroethylene metabolized, it was not possible to determine if trichloroethylene suppressed the metabolism of tetrachloroethylene. Concurrent administration of tetrachloroethylene and trichloroethylene to mice did not result in additive or synergistic effects in induction of hepatic peroxisomal proliferation as measured by cyanide-insensitive palmitoyl CoA oxidation activity (Goldsworthy and Popp 1987). This may be related to preferential metabolism of trichloroethylene at the dose levels used.

Combined oral treatment of rats with tetrachloroethylene (3,000 mg/kg/day) and vitamin E (400 mg/kg/day) prevented the centrilobular necrosis in the liver and hypercellular glomeruli and congestion of convoluted tubules of the kidneys that was observed when rats were treated with tetrachloroethylene alone (Ebrahim et al. 1996). Vitamin E also prevented the tetrachloroethylene-induced increase in protein and protein-bound carbohydrates observed in the liver and kidneys of rats treated only with tetrachloroethylene. This study suggests that free radical metabolites may play a role in the liver and kidney toxicity observed in rats treated with tetrachloroethylene. A follow-up study by this group further examined the potential protective properties of 2DG and vitamin E, as well as taurine,

against tetrachloroethylene-induced membrane damage (Ebrahim et al. 2001). All three treatments reduced the membrane damage caused by tetrachloroethylene.

Tetrachloroethylene may sensitize the myocardium to effects of other chemicals. For example, high doses of intravenously administered tetrachloroethylene have been found to sensitize the myocardium to the presence of exogenous epinephrine (Kobayashi et al. 1982). However, Reinhardt et al. (1973) did not observe sensitization to epinephrine in beagle dogs exposed to vapors of tetrachloroethylene. Tetrachloroethylene may also have a direct effect on the heart. In synergy with alcohol and hypoxia, tetrachloroethylene prolonged atrioventricular conduction in the perfused rat heart. Because of the perfused heart model, this effect was not catecholamine-mediated (Kawakami et al. 1988).

Using the *Tradescantia* micronucleus assay, Ma et al. (1992) examined the genotoxicity of tetrachloroethylene with lead tetraacetate, arsenic trioxide, and dieldrin. Although tetrachloroethylene, dieldrin, and arsenic trioxide were not genotoxic alone, mixtures of tetrachloroethylene with dieldrin or arsenic trioxide were genotoxic. An interaction between tetrachloroethylene and lead tetraacetate was not observed. When mixtures of three chemicals (combination of any three: tetrachloroethylene, dieldrin, arsenic trioxide, and lead tetraacetate) were tested, interactions were also not observed.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to tetrachloroethylene than will most persons exposed to the same level of tetrachloroethylene in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of tetrachloroethylene, or compromised function of organs affected by tetrachloroethylene. Populations who are at greater risk due to their unusually high exposure to tetrachloroethylene are discussed in Section 6.7, Populations with Potentially High Exposures.

The elderly with declining organ function and the youngest of the population with immature and developing organs (i.e., premature and newborn infants) will be more vulnerable to toxic substances in general than healthy adults. As discussed in Section 3.7 (Children's Susceptibility), the developing fetus, children, and especially the developing nervous system may be particularly susceptible to the toxic effects of tetrachloroethylene, potentially due to age-related pharmacokinetic differences. Studies in mice suggest that tetrachloroethylene can cross the placenta and that trichloroacetic acid concentrates in the

fetus (Ghantous et al. 1986). Unmetabolized tetrachloroethylene has been excreted in breast milk and was detected in an exposed infant with liver damage (Bagnell and Ellenberger 1977). As tetrachloroethylene is lipophilic, it is capable of accumulating in the body over time, which may account for the observed increase in dose metrics predicted by PBPK models for later life stages (Clewell et al. 2004). The lipophilicity of tetrachloroethylene may also result in higher accumulations of the compound in exposed persons with higher body fat content; conversely, lower body fat may result in higher blood levels of tetrachloroethylene. There are no data on the potential effects of obesity or underweight on tetrachloroethylene pharmacokinetics. Studies in rats indicate that blood:air and organ:air partition coefficients are elevated in aged male rats compared with adult male or postnatal day 10 male rats, suggesting greater absorption and distribution of tetrachloroethylene among older animals (Mahle et al. 2004); there are no data on tetrachloroethylene partitioning in aged human blood.

Certain ethnic populations may also have increased susceptibility to toxicity based on pharmacokinetics of tetrachloroethylene, as the amount of tetrachloroethylene metabolized varies among different ethnic human populations. Seiji et al. (1989) reported that the relationship between total urinary trichloro-compounds and the concentration of tetrachloroethylene in breath air was 0.063 mg trichloroacetic acid/L per ppm tetrachloroethylene in Chinese workers, while the value was 0.7 mg trichloroacetic acid/L per ppm tetrachloroethylene in Japanese workers. Jang et al. (1997) observed differences in tetrachloro-ethylene metabolism among different ethnic populations between persons of Caucasian and Asian descent in a controlled human exposure study, with higher levels of tetrachloroethylene measured in exhaled breath of Caucasians compared with those of Asian descent. Data on differences in the pharmacokinetic behavior of tetrachloroethylene in people of other ethnicities were not located in the available literature.

Patients who had detectable blood levels of VOCs (often more than one chemical) and who had a variety of systemic symptoms were classified as “chemically sensitive” by Rea et al. (1987). Tetrachloroethylene was the most common chemical detected in the blood of the “chemically sensitive” individuals who were studied (found in 72 of 134 patients). No controls were used in this study, so it is not clear if tetrachloro-ethylene is more frequently detected in chemically sensitive individuals and/or if concentrations of tetrachloroethylene in the blood are greater in sensitive individuals than in the general population. Some adults also appear to have increased sensitivity to certain systemic effects of tetrachloroethylene (e.g., cardiac sensitization) (Abedin et al. 1980). Since high doses of tetrachloroethylene are known to cause liver and kidney effects, persons with clinical or subclinical renal or hepatic disease may be predisposed to the effects of tetrachloroethylene. Persons with preexisting nervous system diseases may also be more sensitive to the neurotoxic effects of tetrachloroethylene.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to tetrachloroethylene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to tetrachloroethylene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to tetrachloroethylene:

Dart RC. 2004. Medical toxicology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1339-1341.

Leikin JB, Paloucek FP. 2002. Poisoning & toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 1212-1213.

Palmer RB, Phillips SD. 2007. Chlorinated hydrocarbons. In: Shannon MW, Borron SW, Burns MJ. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders Elsevier, 1347-1361.

3.11.1 Reducing Peak Absorption Following Exposure

Following suspected overexposure to tetrachloroethylene, the person should be promptly placed under the care of a knowledgeable physician. In the case of vapor exposure, the person should be removed from the vapor-contaminated environment and given the standard emergency and supportive treatment. There is no specific antidote. Anesthetic overexposure may require respiratory assistance and the treatment of cardiac arrhythmias. General recommendations for reducing absorption following acute oral exposure have included the administration of water or milk, gastric lavage, and/or administration of a charcoal slurry with or without a cathartic (Ellenhorn and Barceloux 1988; HSDB 2013; Stutz and Ulin 1992). Induction of emesis is not recommended because of the danger of aspiration resulting in a chemical pneumonitis. In the case of eye exposure, irrigation with copious amounts of water or saline has been recommended (Bronstein and Currance 1988; Haddad and Winchester 1990; HSDB 2013; Leikin and Paloucek 2002; Stutz and Ulin 1992). For dermal exposure, the removal of contaminated clothing and a thorough washing of any exposed areas with soap and water have been recommended (HSDB 2013; Leikin and Paloucek 2002; Stutz and Ulin 1992).

3.11.2 Reducing Body Burden

The body does not retain significant amounts of tetrachloroethylene; most of an absorbed dose is excreted within several days of either inhalation or oral exposure (see Section 3.4.4). However, methods aimed at enhancing elimination during this period of retention may be effective in mitigating the serious effects that can occur following absorption of tetrachloroethylene. One possible method for enhancing elimination is increasing the ventilation rate. In a single case report, controlled hyperventilation over a 5-day period enhanced pulmonary elimination in a 6-year-old boy who had ingested between 12 and 16 g of tetrachloroethylene (Koppel et al. 1985). It is emphasized that no clinical treatments, other than supportive measures, are currently available to enhance elimination.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No clear approaches to interfering with the mechanisms of tetrachloroethylene toxicity have emerged from the available literature. Efforts to do so may be stymied by the limited data and variety of mechanisms postulated for the known target organs (central nervous system, kidney, and liver), as well as the role of pharmacokinetics in the effects on each organ. Specifically, efforts to alter the metabolism of tetrachloroethylene (e.g., to deplete blood levels of parent compound that likely mediate neurotoxicity) via stimulation of oxidative metabolism or glutathione conjugation may shift toxicity from the central nervous system to the liver or kidney, as toxicity to these organs is believed to be mediated by metabolic products from these pathways. Methods for reducing the formation of reactive metabolites in the kidney via inhibition of β-lyase or other enzymes in this pathway may be viable options, but are not currently available for clinical use.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tetrachloroethylene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tetrachloroethylene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would

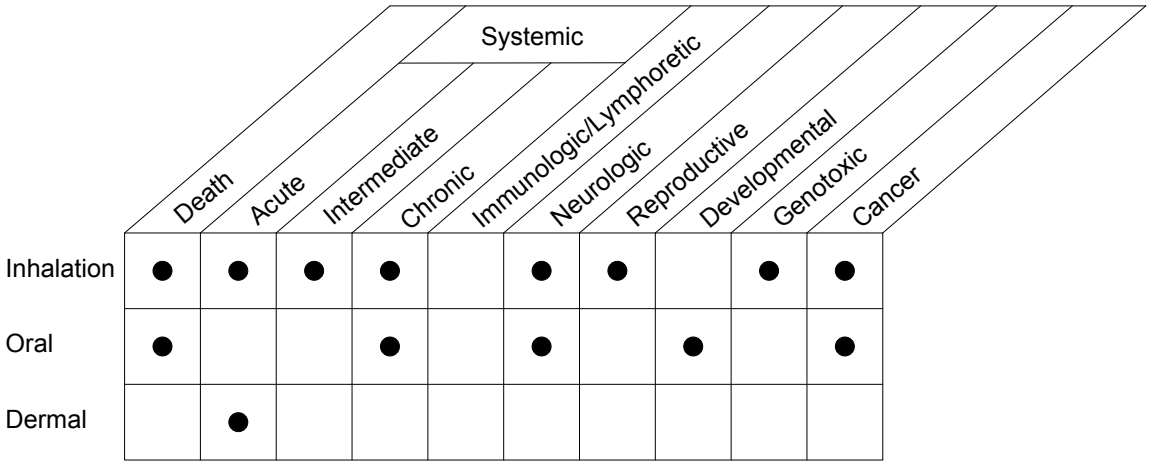
reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Tetrachloroethylene

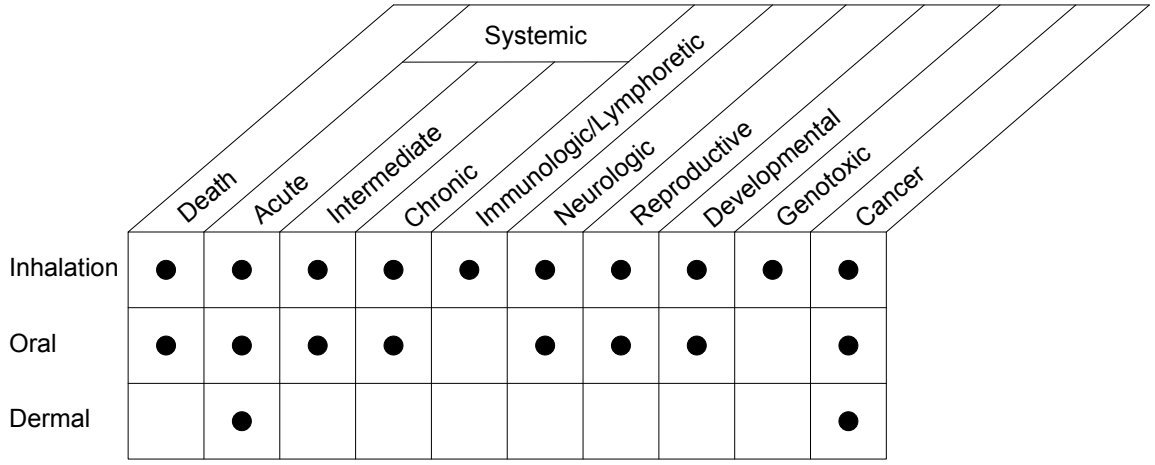
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to tetrachloroethylene are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of tetrachloroethylene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Most of the literature regarding health effects in humans comes from studies of workers exposed to tetrachloroethylene during occupational uses. Limited data are available from residential exposure to tetrachloroethylene from close proximity to dry cleaning establishments and from contaminated drinking water. Case reports describe some of the acute, intermediate, and chronic health effects associated with ingestion or inhalation of the chemical. The predominant mode of exposure in these studies is by inhalation. The primary untoward health effects from acute exposure observed in the humans reported in these occupational and case studies are the result of central nervous system depression or skin injury. According to one case report, direct dermal exposure to tetrachloroethylene reportedly resulted in erythema and blistering of the skin. Transient kidney and liver injury are observed when acute and prolonged exposure to higher vapor concentrations occurs. Acute exposure to high vapor concentrations has also resulted in death, from either profound respiratory center depression or cardiac arrhythmia. Additional effects potentially associated with chronic exposure include loss of color vision, liver and kidney effects, immunological effects, reproductive effects, and cancer. Most of these studies are limited by the inadequate characterization of exposure levels and associated health effects and the lack of control for other chemical exposures, socioeconomic status, alcohol consumption, and tobacco consumption.

Figure 3-6. Existing Information on Health Effects of Tetrachloroethylene



Human



Animal

● Existing Studies

Experimental exposure studies at concentrations achieved in occupational settings have confirmed neurological effects.

A large number of studies examining the health effects of inhalation of tetrachloroethylene by animals were reviewed. There were also a number of studies regarding health effects of ingested tetrachloroethylene. Primary target organs and systems in animals include the nervous system, kidney, and liver. The mouse is especially susceptible to liver damage leading to increased risk of liver cancer. The rat appears to have an increased sensitivity to kidney damage leading to cancers of the kidney. Evidence suggests that tetrachloroethylene exposure during gestation affects growth and development, but is not overtly teratogenic. The limited dermal exposure studies of tetrachloroethylene in animals indicate that the compound can be absorbed following direct application, but the studies have not clearly identified any effects.

3.12.2 Identification of Data Needs

While the database of toxicity information on tetrachloroethylene is adequate for some end points, significant data gaps exist for several end points, including developmental and neurodevelopmental toxicity, and immunotoxicity (in both developmental and in adult populations). Data needs by exposure duration and end point are discussed in further detail below; specific research recommendations include the following:

- Studies of immunotoxicity and immune function in developing and adult animals and/or in human populations exposed to tetrachloroethylene via oral or inhalation routes, for both intermediate and chronic durations;
- Additional studies of developmental and neurodevelopmental endpoints in humans or animals exposed to tetrachloroethylene via oral or inhalation routes;
- Additional oral bioassays evaluating chronic effects and cancer in animals; and
- Studies of tetrachloroethylene effects in humans or animals exposed dermally.

In addition, *in vivo* or *in vitro* research on interactions between tetrachloroethylene and other constituents of commonly-encountered chemical mixtures is needed. Tetrachloroethylene frequently occurs in conjunction with other chlorinated solvents in water from hazardous waste sites (Agency for Toxic Substances and Disease Registry 2004) and in conjunction with other indoor air contaminants (Agency for Toxic Substances and Disease Registry 2007b); however, few data are available on the toxicity of

these mixtures. Finally, research on the potential vulnerability of minority and low-income populations, who may be exposed to multiple health stressors in addition to chemical exposure, would be beneficial.

Acute-Duration Exposure. There are reports on acute tetrachloroethylene exposure of humans and animals following inhalation and oral exposure. The primary targets following acute inhalation and oral exposure are the central nervous system (Altmann et al. 1990, 1992; Carpenter 1937; Haerer and Udelman 1964; Hake and Stewart 1977; Kendrick 1929; Moser et al. 1995; NTP 1986; Ogata et al. 1971; Rowe et al. 1952; Savolainen et al. 1977; Stewart 1969; Stewart et al. 1961a, 1961b, 1970, 1981), kidneys (Goldsworthy and Popp 1987), and liver (Berman et al. 1995; Goldsworthy and Popp 1987; Hake and Stewart 1977; Hanioka et al. 1995; Kylin et al. 1963; Levine et al. 1981; NTP 1986; Odum et al. 1988; Saland 1967; Schumann et al. 1980; Stewart 1969).

The majority of the human studies are cases involving accidental exposure (Garnier et al. 1996; Koppel et al. 1985; Saland 1967), occupational exposure (Levine et al. 1981; Lukaszewski 1979; Morgan 1969; Patel et al. 1973), exposure from the use of tetrachloroethylene as an anthelminthic (Kendrick 1929; Wright et al. 1937), and exposure from contaminated drinking water (Aschengrau et al. 2012; Getz et al. 2012; Janulewicz et al. 2008, 2012). However, studies are available that reported the thresholds for central nervous system effects in humans resulting from acute-duration inhalation exposures to tetrachloroethylene (Altmann et al. 1990, 1992; Carpenter 1937; Hake and Stewart 1977; Rowe et al. 1952). An acute inhalation MRL could be obtained based on the NOAEL of 2 ppm for human central nervous system effects (Altmann et al. 1992); however, PBPK simulations indicate that an MRL obtained from this study would not be adequately protective for exposures up to 2 weeks. Furthermore, since the chronic-duration LOAEL of 2 ppm used to obtain the chronic-duration inhalation MRL is the same value, the chronic value was adopted for the acute-duration inhalation MRL. Human oral exposure data, limited to an accidental exposure (Koppel et al. 1985) and descriptions of the use of tetrachloroethylene as an anthelminthic (Chaudhuri and Mukerji 1947; Kendrick 1929; Koppel et al. 1985; Sandground 1941; Wright et al. 1937) do not clearly define threshold dosages. Direct dermal contact with tetrachloroethylene results in chemical burns (Hake and Stewart 1977; Ling and Lindsay 1971; Morgan 1969). Additional effects in humans following dermal exposure only have not been conclusively identified.

There are acute inhalation studies that provide data on lethality (Friberg et al. 1953; NTP 1986) and systemic effects in mice including neurotoxic (NTP 1986), hepatic (Kylin et al. 1963; NTP 1986; Odum et al. 1988), respiratory (Aoki et al. 1994), and immunotoxic effects (Aranyi et al. 1986), as well as neurotoxic effects in rats (Albee et al. 1991; Boyes et al. 2009; Goldberg et al. 1964; Mattson et al. 1998;

NTP 1986; Rowe et al. 1952; Savolainen et al. 1977). There are also oral lethality studies in rats (Berman et al. 1995; Hayes et al. 1986) and mice (Philip et al. 2007; Wenzel and Gibson 1951). Effects noted in acute oral studies of tetrachloroethylene in animals include increased liver weight (Berman et al. 1995; Goldsworthy and Popp 1987; Hanioka et al. 1995), nephropathy (Goldsworthy et al. 1988; Potter et al. 1996), decreased body weight gain in rats (Schumann et al. 1980), neurological effects in rats (Moser et al. 1995; Warren et al. 1996), and liver hypertrophy (Schumann et al. 1980) in mice. Interpretation of some of these data is difficult because of limitations in the design and conduct of the studies (e.g., decreased survival, poor study methodology).

Oral exposure of young mice to tetrachloroethylene resulted in hyperactivity when the mice were tested as adults (Fredriksson et al. 1993); however, metabolic differences between mice and humans exposed orally suggest that mice would be a poor model for neurotoxicity in humans. The chronic-duration oral MRL of 0.008 mg/kg/day has been adopted as the acute-duration oral MRL based on PBPK modeling results that predict that neurological effects would occur at the same concentration after acute and chronic exposures. Acute dermal exposure data in animals were not identified. Additional data on dermal exposure of animals would be useful to provide threshold levels. The targets that seem to be of greatest concern following tetrachloroethylene exposure are the central nervous system, including effects on the developing nervous system, the liver, and the kidneys. Populations living near hazardous waste sites may experience acute-duration exposures to tetrachloroethylene via inhalation, oral, or dermal routes as a result of accidental releases.

Intermediate-Duration Exposure. Human data regarding intermediate-duration exposure are limited to inhalation studies that reported adverse neurological effects (Abedin et al. 1980; Meckler and Phelps 1966) and cardiac sensitization (Abedin et al. 1980). However, exposure concentrations are not well defined in these studies. As with the acute-duration inhalation MRL, the intermediate-duration inhalation MRL was set equal to the chronic-duration inhalation MRL (using human data) based on PBPK simulations. No human data were located regarding oral or dermal exposure to tetrachloroethylene. The target organs identified in animal studies of intermediate-duration oral or inhalation exposure to tetrachloroethylene include the nervous system (Carpenter 1937; Karlsson et al. 1987; Kyrklund et al. 1988; Mattsson et al. 1992, 1998; Rosengren et al. 1986), liver (Boverhof et al. 2012; Buben and O'Flaherty 1985; Carpenter 1937; Hayes et al. 1986; Jonker et al. 1996; Kjellstrand et al. 1984; Kylin et al. 1965; Kyrklund et al. 1988; NTP 1986; Odum et al. 1988; Philip et al. 2007; Rajamanikandan et al. 2012; Rowe et al. 1985; Story et al. 1986), kidney (Carpenter 1937; Ebrahim et al. 1996; Green et al. 1990; Hayes et al. 1986; Jonker et al. 1996; NTP 1986; Rowe et al. 1985), and immune

system (Seo et al. 2008a, 2012). These studies were conducted in a variety of animal species including mice, rats, guinea pigs, and gerbils. No intermediate-duration dermal studies in animals were located.

The chronic-duration oral MRL of 0.008 mg/kg/day has been adopted as the intermediate-duration oral MRL based on PBPK modeling results indicating that neurological effects occur at the same concentration after acute, intermediate, and chronic exposures. The lowest animal LOAEL was for neurological effects in rats (Chen et al. 2002). After conversion to a human equivalent dose, the LOAEL (1.8 mg/kg/day) from Chen et al. (2002) is equivalent to the LOAEL (2.3 mg/kg/day) for chronic human exposure used to obtain the chronic oral MRL; thus, because the chronic value was derived from human data, the chronic-duration oral MRL was adopted as the intermediate-duration oral MRL. Additional animal studies concerning the threshold of nervous system effects following inhalation, oral, and dermal exposure to tetrachloroethylene would be especially useful for determining levels of significant exposure to tetrachloroethylene that are associated with adverse health effects.

Two oral exposure studies in rats and mice (Seo et al. 2008a, 2012) have suggested that very low levels of tetrachloroethylene in the drinking water of rodents may enhance the immune response to allergens and exacerbate inflammation. The toxicological importance of these findings and their relevance to humans are uncertain, and available human data on immune system end points are inadequate to inform these questions. Additional human epidemiological studies, animal studies, and *in vitro* investigations of potential immune system perturbations are needed to confirm the findings of Seo et al. (2008a, 2012) and/or to further evaluate functional immune system effects of tetrachloroethylene exposure.

Chronic-Duration Exposure and Cancer. Kidney toxicity (Bundschuh et al. 1993; Franchini et al. 1983; Mutti et al. 1992; Price et al. 1995; Vyskocil et al. 1990), liver toxicity (Brodkin et al. 1995; Coler and Rossmiller 1953), immunotoxicity (Andrys et al. 1997; Emara et al. 2010), and symptoms of chronic encephalopathy (Gregersen 1988) were reported in studies of humans occupationally exposed to tetrachloroethylene. Other occupational exposure studies have not identified kidney (Lauwerys et al. 1983; Solet and Robins 1991) or irreversible central nervous system effects (Cai et al. 1991; Coler and Rossmiller 1953; Lauwerys et al. 1983). Deficits in behavioral tests that measured short-term memory for visual designs (Echeverria et al. 1995) have been noted in humans occupationally exposed to tetrachloroethylene. There are conflicting reports on the effect of tetrachloroethylene on color vision in persons occupationally exposed to tetrachloroethylene. Cavalleri et al. (1994) reported an effect on color vision at an average concentration of 7.3 ppm, while Nakatsuka et al. (1992) reported no effect on color vision at average concentrations of 15.3 and 10.7 ppm for men and women, respectively. Further

evaluation of the Cavalleri et al. (1994) cohort revealed that workers whose exposure to tetrachloroethylene had increased demonstrated further decrements in color vision, while those whose exposure had decreased had no changes in color vision (Gobba et al. 1998). Other studies indicate that color vision may be impaired in workers or offspring following occupational tetrachloroethylene exposure (Sharanjeet-Kaur et al. 2004; Till et al. 2003), but these studies did not quantify exposure levels. Further studies to evaluate the dose-response relationship between exposure to tetrachloroethylene and color vision would be useful. Ferroni et al. (1992) reported increased reaction times in women exposed to tetrachloroethylene in dry cleaning shops at an average concentration of 15 ppm for about 10 years.

A study of neurological function in persons living above or next to dry cleaning facilities has been completed (Altmann et al. 1995). Although no differences in absolute values of neurological function tests were noted, effects on neurological function tests were observed when multivariate analysis was used to analyze the data. Deficits in visual contrast sensitivity, but not in color discrimination, were observed in children or adults living in residential buildings that also housed dry cleaning facilities (Schreiber et al. 2002; Storm et al. 2011). Studies in residential populations suggested effects at lower concentrations than studies in occupational populations, but were not considered adequate for MRL derivation. Thus, further studies of larger residential populations exposed to very low levels of tetrachloroethylene would be useful. In addition, studies of tetrachloroethylene effects in potentially susceptible populations, including minority and low-income populations who may be exposed to multiple health stressors in addition to chemical exposure, may serve to inform or refine the MRL. As there are few studies of health effects in human populations exposed to tetrachloroethylene orally, additional investigation of such populations would serve to fill this data gap.

Adverse health effects observed in chronic inhalation animal studies include reduced survival in rats and mice (NTP 1986), biochemical alterations in the brains of gerbils (Briving et al. 1986; Kyrklund et al. 1984), and kidney effects (nephropathy) in rats and mice (NTP 1986). Chronic oral animal studies have demonstrated reduced survival and kidney effects in rats and mice (NCI 1977). Doses causing target organ effects in animals following oral exposure are very similar to those causing lethality (NCI 1977). No chronic dermal studies were located. Additional chronic studies in animals that provide information on threshold levels and dose-response relationships for toxic effects following oral or dermal exposure would be useful since populations living near hazardous waste sites are likely to be exposed at low levels over a long period of time.

Epidemiology studies suggest a possible association between chronic inhalation exposure to tetrachloroethylene and cancer (Anttila et al. 1995; Blair et al. 1979, 1990; Boice et al. 1999; Brown and Kaplan 1987; Chapman et al. 1981; Chang et al. 2003; Duh and Asal 1984; Katz and Jowett 1981; Lipworth et al. 2011; Lynge and Thygesen 1990; Lynge et al. 2006; Ma et al. 2009; Ruder et al. 1994, 2001; Spirtas et al. 1991). The cancer types most consistently showing an increase were bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma (reviewed by NRC 2010; EPA 2012a). In general, studies examining other cancer types are confounded by concomitant exposure to other solvents and lack of consideration of the smoking habits and socioeconomic status of the subjects. The only data on carcinogenicity in humans following chronic oral exposure to tetrachloroethylene are from communities exposed to drinking water contaminated with tetrachloroethylene (Aschengrau et al. 1998, 2003; Cohn et al. 1994; Gallagher et al. 2011; Lagakos et al. 1986; Paulu et al. 1999; Viera et al. 2005). There are a number of confounding factors (i.e., uncertain exposure duration, exposure to multiple organic compounds) that render the studies problematic, and the findings do not substantiate an association between tetrachloroethylene and cancer in humans. Nested case-control studies within a cohort exposed to tetrachloroethylene in drinking water suggested a potential association between tetrachloroethylene exposure and breast cancer (Aschengrau et al. 1998, 2003; Gallagher et al. 2011; Viera et al. 2005), but not other types of cancers (Paulu et al. 1999). No chronic dermal exposure data are available for humans.

Inhalation and oral bioassays using rats and mice have been conducted (JISA 1993; NCI 1977; NTP 1986). These data provide sufficient evidence to conclude that tetrachloroethylene is carcinogenic in animals. However, the oral study (NCI 1977) was limited by control groups smaller than treatment groups, decreased survival, and dose adjustments during the study. A dermal study conducted in mice reported no incidence of cancer in the test animals (Van Duuren et al. 1979). No additional cancer bioassays in animals appear to be necessary at this time. However, additional mechanistic data to aid interpretation of the mouse liver tumors and rat mononuclear cell leukemias and their relevance to humans would be useful. In addition, research investigating the potential contribution of inflammation to adverse effects of chronic tetrachloroethylene exposure (including cancers as well as liver, kidney, and neurological effects) would be beneficial in light of the data from Seo et al. (2008a) suggesting enhancement of inflammation in rats exposed to this compound.

Genotoxicity. *In vivo* genotoxicity studies examining human lymphocytes (Ikeda et al. 1980; Seiji et al. 1990) or leukocytes (Toraason et al. 2003) from persons occupationally exposed to tetrachloroethylene (Ikeda et al. 1980; Seiji et al. 1990) were negative for sister chromatid exchange; however, one study reported an increase in transient DNA damage (acentric DNA fragments) that correlated with the TWA

blood levels of tetrachloroethylene in dry cleaners (Tucker et al. 2011). The majority of *in vivo* animal assays (Cedaerburg et al. 2010; Murakami and Horikawa 1995; Toraason et al. 1999) and *in vitro* genotoxicity tests using prokaryotic cells (Bartsch et al. 1979; Emmert et al. 2006; Haworth et al. 1983; NTP 1986; Shimada et al. 1983; Watanabe et al. 1998), eukaryotic cells (Bronzetti et al. 1983; Callen et al. 1980; Koch et al. 1988), or mammalian cells (Costa and Ivanetich 1980; Hartman and Speit 1995; Matsushima et al. 1999; Mazzullo et al. 1987; NIOSH 1980; NTP 1986; Shimada et al. 1983; Tu et al. 1985; Walles 1986) showed negative or marginal results for gene mutation, recombination, DNA damage, micronuclei, and sister chromatid exchange. Although the results in both *in vivo* and *in vitro* assays generally indicate that tetrachloroethylene is not genotoxic, marginal and equivocal results in some assays indicate that genotoxic effects cannot be ruled out. Data are available indicating that the precursor of the *N*-acetyl cysteine derivative of tetrachloroethylene, *S*-(1,2,2-trichlorovinyl)glutathione, induces a powerful mutagenic effect in *S. typhimurium* strains in the presence of rat kidney fractions (Vamvakas et al. 1989). It is conceivable, therefore, that the mutagenic potential of the parent compound could be uncovered if the steps involved in the activation of tetrachloroethylene via glutathione conjugation could be replicated in *in vitro* microbial systems. Additional genotoxicity assays would be useful for either substantiating the data that indicate that this chemical may be carcinogenic in humans or providing information about the carcinogenic mechanism of tetrachloroethylene. Additional data on genotoxic end points from animals exposed *in vivo* would be useful because the available data are inconclusive.

Reproductive Toxicity. Reproductive data are available on women occupationally exposed to tetrachloroethylene in dry cleaning operations. Some studies suggest an increase in spontaneous abortion (Ahlborg 1990; Bosco et al. 1986; Doyle et al. 1997; Hemminki et al. 1980; Kyyrönen et al. 1989; Lindbohm et al. 1990; Windham et al. 1991), but other studies reported no increase (McDonald et al. 1986, 1987; Olsen et al. 1990). Limited evidence also suggests that time-to-pregnancy may be increased among women occupationally exposed to tetrachloroethylene (Sallmen et al. 1995). Wives of dry cleaners who had significantly more rounded sperm did not have more spontaneous abortions, although there was some evidence that it may take slightly longer for these women to become pregnant (Eskenazi et al. 1991a, 1991b). Similarly, paternal occupational exposure to tetrachloroethylene was associated with decreased fecundability, but not increased rates of spontaneous abortion (Sallmén et al. 1998; Taskinen et al. 1989). These studies suggest that tetrachloroethylene may affect the ability of men to reproduce. Collectively, these occupational studies are limited by inadequate information on exposure levels, limited controls for life-style factors, the difficulty in identifying appropriate controls, and the problems in controlling for concomitant exposures to other chemicals. No studies were located regarding reproductive effects in humans after oral or dermal exposure to tetrachloroethylene.

Evidence from a limited number of well-conducted reproductive studies in laboratory animals, including a multigenerational study, suggests that tetrachloroethylene is a potential female reproductive toxicant following inhalation exposure. Exposure to concentrations ≥664 ppm resulted in decreased numbers of liveborn pups, increased pre- and postimplantation losses, and increased resorptions (Szakmáry et al. 1997; Tinston 1995). These exposure levels also resulted in maternal toxicity (e.g., frank neurological toxicity, reduced maternal weight gain). A significant increase in resorptions was also observed in rats treated by gavage with tetrachloroethylene during organogenesis at 900 mg/kg/day, a dose that resulted in maternal ataxia and decreased body weight gain (Narotsky and Kavlock 1995). These studies suggest that reproductive effects following inhalation or oral exposure are unlikely to occur at exposure levels below those that result in maternal toxicity. No studies were located regarding reproductive effects in animals following dermal exposure.

There is also limited evidence that tetrachloroethylene can damage both male and female gametes. Spermhead abnormalities were observed in mice, but not rats, 4 and 10 weeks following a 5-day exposure to 500 ppm tetrachloroethylene (NIOSH 1980), and decreased oocyte quality was reported in rats exposed to 1,700 ppm tetrachloroethylene for 2 weeks (Berger and Homer 2003). However, histopathological effects in the testes and ovaries were not observed in rats or mice exposed by gavage to tetrachloroethylene at doses that resulted in increased mortality (NCI 1977).

There is a need to further assess relationships between exposure to tetrachloroethylene and reproductive outcomes among humans following occupational exposure, and studies should be conducted to assess if there is a reproductive risk associated with consuming contaminated drinking water. It would be useful to conduct multigeneration or continuous breeding studies for oral and dermal exposures of animals in order to clarify the potential for tetrachloroethylene to cause reproductive effects in humans via these exposure routes.

Developmental Toxicity. A human epidemiological study examined birth outcomes associated with maternal residence in Endicott, New York, an area where soil was contaminated with VOCs (Forand et al. 2012). In a region primarily contaminated with tetrachloroethylene, there was a nonsignificant elevation in the relative risk for cardiac defects compared with state-wide incidence (excluding New York City). This study is limited by the small number of births in the study area, lack of control for potential occupational exposure to tetrachloroethylene, lower socioeconomic status in the study area than the general comparison population, and concurrent exposure to other VOCs.

A prospective population-based cohort study in Jerusalem suggests parental exposure to tetrachloroethylene may lead to the development of neurological disorders in offspring, as the diagnosis of schizophrenia in children of dry cleaners almost tripled compared with the general population (Perrin et al. 2007). Limitations of this study include a small number of diagnosed cases (n=4), lack of exposure data, and lack of control for family history of mental illness, an important risk factor for developing schizophrenia. Studies examining the association between drinking water contamination and birth outcome (Aschengrau et al. 2008, 2009; Bove et al. 1995; Lagakos et al. 1986; Sonnenfeld et al. 2001) have suggested that tetrachloroethylene exposure may be associated with increased ocular and auditory defects, central nervous system abnormalities, oral cleft defects, neural tube defects, low birth weight, and small-for-gestational age. Additional negative outcomes in these studies include evidence for impaired immunity (Lagakos et al. 1986) and increased risk for mental illness in adulthood (Aschengrau et al. 2012) following exposure during early life stages. These studies are not conclusive because the water was contaminated with other solvents in addition to tetrachloroethylene.

Evidence from multiple studies in laboratory animals indicates that gestational exposure to tetrachloroethylene via inhalation affects growth and development, but that tetrachloroethylene is not teratogenic. Developmental effects have been reported in rats, mice, and rabbits at concentrations as low as 300 ppm, and include growth retardation and skeletal (e.g., delayed ossification) and soft tissue (e.g., kidney dysplasia) anomalies (Carney et al. 2006; Schwetz et al. 1975; Szakmáry et al. 1997; Tepe et al. 1980). These effects often occur at concentrations that illicit maternal toxicity. Following oral exposure, increased postnatal deaths and increased micro/anophthalmia were observed in the offspring of rats treated by gavage with tetrachloroethylene during organogenesis at 900 mg/kg/day, a dose that resulted in maternal ataxia and decreased body weight gain (Narotsky and Kavlock 1995).

There is conflicting evidence regarding the potential for long-term neurobehavioral deficits following gestational exposure. In a combined teratogenic and neurodevelopmental study, female rats were exposed to tetrachloroethylene at 0 or 1,000 ppm 2 weeks prior to mating through gestation day 20, prior to mating through confirmation of pregnancy only, or gestation days 1–20 only (Manson et al. 1981). Regardless of the treatment paradigm, none of the offspring exhibited alterations in survival, growth, neurobehavior, or gross pathologies following observation up to 18 months of age. In contrast, behavioral and neurochemical alterations were observed in rats after maternal exposure to 900 ppm tetrachloroethylene (Nelson et al. 1980). Following oral exposure of mice to 5 mg tetrachloroethylene/kg for 7 days beginning at 10 days of age, hyperactivity was observed at 60 days of age, but not at 17 days of age

(Fredriksson et al. 1993). This study suggests possible permanent damage to the nervous system if exposure occurs during development. No NOAEL was identified. Because the Fredriksson et al. (1993) study serves as the basis for the acute oral MRL, additional animal inhalation and oral studies confirming the observation of developmental neurotoxicity would be useful. Studies in more than one species and studies examining whether the effect is a result of tetrachloroethylene or trichloroacetic acid are needed to determine if the results in mice are applicable to predicting effects in humans.

No studies were located regarding developmental effects following dermal exposure to tetrachloroethylene in animals. Additional animal studies should focus on the mechanism by which tetrachloroethylene produces embryotoxic and neurological effects in the offspring. Studies examining the relationship between behavioral effects and morphological changes in the nervous system following tetrachloroethylene exposure would be especially useful. Because tetrachloroethylene crosses into breast milk (Byczkowski and Fisher 1994), and because workers exhale tetrachloroethylene at home, these animal studies should also examine the later stages of nervous system development that occur after birth. Nervous system function should be examined throughout the lifetime of exposed animals to determine if effects are consistently observed as the animals age. Additional studies regarding developmental effects in animals following inhalation, oral, and dermal exposure would provide useful information relevant to humans exposed by these routes in areas near hazardous waste sites.

Immunotoxicity. The available studies of immunological effects in humans exposed to tetrachloroethylene provide suggestive evidence for alterations in cytokine signaling related to hypersensitivity; however, the data are limited. Egyptian dry cleaners exposed to <140 ppm tetrachloroethylene demonstrated increased serum and cellular IL-4 levels and serum IgE levels compared to age- and lifestyle-matched referent subjects (Emara et al. 2010). In a study examining a wide variety of VOCs, Lehmann et al. (2002) reported decreased percentages of IFN-γ-producing T cells in the umbilical cord blood of infants from homes with higher levels of tetrachloroethylene (>7.3 μg/m^3, the 75th percentile concentration) compared with infants from homes with lower levels (Lehmann et al. 2002). The limited available epidemiological studies investigating allergic sensitization and asthma have not observed a clear role for tetrachloroethylene exposure in the development of these conditions (Delfino et al. 2003; Lehmann et al. 2001), but a case report of hypersensitivity pneumonitis in a female dry cleaner provides some support (Tanios et al. 2004).

A very small cohort study reported statistically significant alterations in a number of blood immunological parameters when dry cleaning workers with high tetrachloroethylene exposure were

compared with measurements from a referent group of "administrators" or when compared with laboratory reference values (Andrys et al. 1997). However, the small number of subjects limits the interpretation of these findings. Available data indicate possible immunotoxic effects (altered ratios of T lymphocyte subpopulations) in humans chronically exposed to tetrachloroethylene (21 ppb) as well as trichloroethylene (267 ppb) and other solvents from a contaminated water supply (Byers et al. 1988). However, because of other contaminants, it is not possible to infer from these data the exact role of tetrachloroethylene.

Findings of immunological effects following tetrachloroethylene exposure in animals are inconsistent. No evidence of immunotoxicity was reported following inhalation exposure in rats (Boverhof et al. 2012). One study (Aranyi et al. 1986) in which mice were exposed by inhalation for 3 hours to varying doses of tetrachloroethylene demonstrated increased susceptibility to bacterial infection. Interpretation of this study is complicated by the fact that the controls for one of the treated groups had a higher mortality rate than any other group in the study. Atrophy of the spleen and thymus was reported in rats following exposure to 2,000 mg tetrachloroethylene/kg for 5 days (Hanioka et al. 1995). In a study in which rats were exposed to tetrachloroethylene vapors, no production of antibodies to tetrachloroethylene was detected (Tsulaya et al. 1977). In a 14-day study, histopathological changes in the spleen and thymus gland were not observed in rats treated by gavage with tetrachloroethylene at a dose that resulted in liver effects (Berman et al. 1995). No effects on natural killer cell, natural cytotoxic, and natural P815 killer cell activities or humoral and T cell mitogenesis were observed in cells harvested from rats and mice treated with three daily intraperitoneal doses of 829 mg tetrachloroethylene/kg (Schlichting et al. 1992). Seo et al. (2008a, 2012) observed enhanced immune response to allergens in rats and mice exposed orally to very low doses of tetrachloroethylene; Seo et al. (2008a) also observed exacerbation of inflammation in skin lesions, as well as enhanced expression of the pro-inflammatory cytokine IL-4, when rats were exposed to tetrachloroethylene for 2 and 4 weeks (respectively). There are no dermal studies regarding the immunotoxic effects of tetrachloroethylene.

Further study of the immune system effects of tetrachloroethylene is needed, given: (1) the effects suggested by the studies of Seo et al. (2008a, 2012); (2) the observation in human epidemiological studies of potential associations between tetrachloroethylene and immune system cancers (multiple myeloma and lymphoma); (3) the potential role of enhanced inflammation in the observed effects of tetrachloroethylene on other systems including the liver, kidney, and neurological system; and (4) evidence that the related compound trichloroethylene exerts immunotoxic effects. A comprehensive immunotoxicity evaluation, including a range of functional tests, is warranted.

Neurotoxicity. It has been clearly established that the central nervous system is a target of tetrachloroethylene toxicity in humans and animals following either inhalation or oral exposure. Human data are available for acute inhalation exposure (Altmann et al. 1990, 1992; Carpenter 1937; Hake and Stewart 1977; Morgan 1969; Rowe et al. 1952; Saland 1967; Stewart et al. 1961b, 1970, 1981) and acute oral exposure (Haerer and Udelman 1964; Kendrick 1929; Koppel et al. 1985; Sandground 1941; Wright et al. 1937) to tetrachloroethylene. The human studies indicate that the LOAEL for neurological effects (increased latency of pattern reversal visual-evoked potentials and deficits for vigilance and eye-hand coordination) following inhalation exposure is about 50 ppm for 4-hour exposures (Altmann et al. 1990, 1992). Additional nervous system effects including dizziness, headache, sleepiness, and incoordination have been observed following 5.5–7-hour exposures at 100–200 ppm in air (Carpenter 1937; Hake and Stewart 1977; Morgan 1969; Rowe et al. 1952; Saland 1967; Stewart et al. 1961b, 1970). Some human studies indicate that chronic occupational exposure to tetrachloroethylene can produce more serious effects, including memory deficits (Cai et al. 1991; Echeverria et al. 1995; Gregersen 1988; Seeber 1989), disorientation (Coler and Rossmiller 1953), and loss of color vision (Cavalleri et al. 1994 Gobba et al. 1998; Sharanjeet-Kaur et al. 2004; Till et al. 2003). Suggestive evidence for an association with Parkinson's disease (Goldman et al. 2012) and schizophrenia (Perrin et al. 2007) has also been reported in small human epidemiological studies. A study of neurological function in persons living above or next to dry cleaning facilities has been completed (Altmann et al. 1995). Although no differences in absolute values of neurological function tests were noted, effects on neurological function tests were observed when multivariate analysis was used to analyze the data. Deficits in visual contrast sensitivity, but not color discrimination, were observed in children or adults living in residential buildings that also housed dry cleaning facilities (Schreiber et al. 2002; Storm et al. 2011). Further studies of larger residential populations exposed to very low levels of tetrachloroethylene would be useful to confirm or refute these findings. Effects observed in humans after acute oral exposure appear to parallel those observed after inhalation exposure (Haerer and Udelman 1964; Kendrick 1929; Koppel et al. 1985; Sandground 1941; Wright et al. 1937). Chronic exposure to tetrachloroethylene via contaminated drinking water during childhood has been associated with increased risk for mental illness and risky behavior later in life (Aschengrau et al. 2011) and impaired color vision (Getz et al. 2012); however, exposure did not affect the frequency of learning, behavior, or attention (Janulewicz et al. 2008, 2012). These studies are limited by small group sizes. No dermal data were located for humans.

Adverse neurological effects in animals exposed to tetrachloroethylene by inhalation include biochemical alterations in the brains of rats (Kyrklund et al. 1988; Wang et al. 1993) and gerbils (Briving et al. 1986;

Karlsson et al. 1987; Kyrklund et al. 1984; Rosengren et al. 1986), electrophysiological changes in rats (Albee et al. 1991; Boyes et al. 2009; Mattsson et al. 1992, 1998), ataxia in rats (Goldberg et al. 1964; NTP 1986), hypoactivity in rats (NTP 1986; Tinston 1995), hyperactivity in rats (Savolainen et al. 1977), and impaired attention in rats (Oshiro et al. 2008). Signs of central nervous system depression (Jonker et al. 1996), ataxia (Narotsky and Kavlock 1995), increased lacrimation, gait changes, and decreased activity (Moser et al. 1995), and impaired operant learning (Warren et al. 1996) have been reported in rats following acute oral exposure to tetrachloroethylene. Oral exposure for 8 weeks resulted in impairments in nociception, increased seizure threshold, and reduced locomotor activity in rats (Chen et al. 2002). No animal data were located regarding neurological effects following dermal exposure to tetrachloroethylene. Animal studies on the mechanism of tetrachloroethylene neurotoxicity would be useful for mitigating the effects observed. Because studies (Fredriksson et al. 1993; Nelson et al. 1980) suggest that tetrachloroethylene is a developmental neurotoxicant, further animal studies would be useful to determine if the developing nervous system is indeed the most sensitive target of tetrachloroethylene.

Epidemiological and Human Dosimetry Studies. The epidemiological data for inhalation exposure to tetrachloroethylene derive predominately from exposures in the workplace, where potential associations have been reported between tetrachloroethylene exposure and cancer (Anttila et al. 1995; Blair et al. 1979, 1990; Boice et al. 1999; Brown and Kaplan 1987; Chang et al. 2003; Chapman et al. 1981; Duh and Asal 1984; Katz and Jowett 1981; Lipworth et al. 2011; Lynge and Thygesen 1990; Lynge et al. 2006; Ruder et al. 1994, 2001), kidney effects (Bundschuh et al. 1993; Franchini et al. 1983; Mutti et al. 1992; Price et al. 2005; Vyskocil et al. 1990), liver effects (Brodkin et al. 1995; Coler and Rossmiller 1953), cardiovascular effects (Abedin et al. 1980; Hake and Stewart 1977), neurological effects (Cavalleri et al. 1994; Echeverria et al. 1995; Ferroni et al. 1992; Gobba et al. 1998; Nakatsuka et al. 1992; Sharanjeet-Kaur et al. 2004; Till et al. 2003), immunological effects (Andrys et al. 1997; Emara et al. 2010), and reproductive effects (Ahlbor 1990; Bosco et al. 1986; Doyle et al. 1997; Eskenazi et al. 1991a, 1991b; Hemminki et al. 1980; Kyyronen et al. 1980; Lindbohm et al. 1990; Sallmen et al. 1995, 1998; Windham et al. 1991). There are a limited number of epidemiological studies suggesting potential associations between living in close proximity to dry cleaning establishments and cancer (Ma et al. 2009) and neurological effects (Altmann et al. 1995; Schreiber et al. 2002; Storm et al. 2011). Most studies do not include adequate characterization of exposure levels and associated health effects, and lack control for other chemical exposures, socioeconomic status, alcohol consumption, and tobacco consumption. Epidemiological data for oral exposure to tetrachloroethylene are available from studies of tetrachloroethylene in the drinking water, where tetrachloroethylene has been associated with breast cancer (Aschengrau et al. 1998, 2003; Gallagher et al. 2011; Viera et al. 2005), neurological effects (Aschengrau

et al. 2011, 2012; Getz et al. 2012; Perrin et al. 2007), immunological effects (Byers et al. 1998; Lagakos et al. 1986), and developmental effects (Aschengrau et al. 2008, 2009; Bove et al. 1995; Forand et al. 2012; Lagakos et al. 1986; Sonnenfeld et al. 2001. These studies are limited by a number of confounding factors (e.g., uncertain exposure duration, exposure to multiple organic compounds). There are also human studies that measured the concentration of tetrachloroethylene in exhaled air to determine exposure concentration (Jang et al. 1993; Monster et al. 1983; Ohtsuki et al. 1983; Solet et al. 1990; Stewart et al. 1977, 1981; Storm et al. 2011).

Additional epidemiological studies are needed that focus on the effects of low levels of tetrachloroethylene in the air, water, or soil near hazardous waste sites. These studies should carefully consider possible confounding factors, including exposure to multiple chemicals, smoking and drinking habits, age, and gender. The end points that need to be carefully considered are kidney and liver effects, cardiovascular effects, developmental effects, neurological effects, immunological effects, and cancer.

Exposure to tetrachloroethylene may occur in the workplace, near hazardous waste sites, and from certain consumer products, including clothes that have been dry cleaned. Most occupational exposure results from inhalation of tetrachloroethylene. Several epidemiological studies have been conducted that provide evidence of relationships between tetrachloroethylene exposure in dry cleaning workers and cancer (Anttila et al. 1995; Blair et al. 1979, 1990; Brown and Kaplan 1987; Chapman et al. 1981; Duh and Asal 1984; Katz and Jowett 1981; Lynge and Thygesen 1990; Ruder et al. 1994), kidney effects (Bundschuh et al. 1993; Franchini et al. 1983; Mutti et al. 1992; Vyskocil et al. 1990), liver effects (Brodkin et al. 1995; Coler and Rossmiller 1953), and cardiovascular effects (Abedin et al. 1980; Hake and Stewart 1977). Limitations of these studies include exposure to other chemicals, lack of control for socioeconomic status, alcohol consumption, and tobacco consumption. There are also human studies that measured the concentration of tetrachloroethylene in exhaled air to determine exposure concentration (Jang et al. 1993; Monster et al. 1983; Ohtsuki et al. 1983; Solet et al. 1990; Stewart et al. 1977, 1981). Additional epidemiological studies might focus on populations exposed to tetrachloroethylene through contaminated drinking water or vapor intrusion in areas surrounding hazardous waste sites in order to determine the effects of chronic, low-level exposures. It would be important for these studies to focus on cancer, reproductive effects, developmental effects, kidney effects, liver effects, and neurological effects, and to document possible confounding factors including other chemical exposures, smoking habits, and gender.

Biomarkers of Exposure and Effect. Exposure to tetrachloroethylene does not produce a unique clinical disease state. However, various central nervous system effects (e.g., dizziness, headache, incoordination, and sleepiness) can result from both inhalation and oral exposure to tetrachloroethylene.

Methods are available that can measure levels of tetrachloroethylene or its metabolites in the blood (Antoine et al. 1986; Michael et al. 1980; Ramsey and Flanagan 1982; Ziglio et al. 1984), urine (Christensen et al. 1988; Michael et al. 1980; Pekari and Aitio 1985a, 1985b), and exhaled air (Wallace et al. 1986a, 1986b). Measurement of tetrachloroethylene in exhaled air is simple, effective, and noninvasive and has been found to be more accurate than measuring metabolites, which are not specific for tetrachloroethylene exposure (Krotoszynski et al. 1979; Monster and Smolders 1984; Wallace 1986). Additional studies that couple measurement of tetrachloroethylene with tests for determining central nervous system effects and other effects (e.g., liver and kidney effects) would be useful to correlate exposure with adverse effects of tetrachloroethylene. This correlation would be useful for monitoring persons possibly exposed to tetrachloroethylene in areas surrounding hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. The data indicate that inhalation is the principal occupational route of exposure for humans, and inhalation and oral exposure from contaminated water supplies is a concern for the general public. Absorption rates suggest that tetrachloroethylene is rapidly and readily absorbed following oral exposure (Frantz and Watanabe 1983; Koppel et al. 1985; Pegg et al. 1979; Schumann et al. 1980) or inhalation (Hake and Stewart 1977; Monster et al. 1979). Tetrachloroethylene vapor is not well absorbed across the skin (McDougal et al. 1990; Riihimaki and Pfaffli 1978), but tetrachloroethylene placed directly on the skin can be absorbed (Bogen et al. 1992; Jakobson et al. 1982; Kinkead and Lehy 1987; Stewart and Dodd 1964; Tsurata 1975). Available data indicate that during inhalation exposure, uptake is influenced more by lean body mass than by ventilation rate and that the absorption rate decreases with increased exposure duration (Monster et al. 1979). Oral studies in animals that examine the stability of tetrachloroethylene to gastrointestinal microbes and rates of absorption from various sections of the gastrointestinal tract would be useful. Further quantitative data regarding the absorption of tetrachloroethylene following direct skin exposure would be useful because of the potential for dermal exposure at a hazardous waste site.

Several studies are available that describe the distribution of tetrachloroethylene in both humans and animals following inhalation exposure (Chen and Blancato 1987; Ghantous et al. 1986; Guberan and Fernandez 1974; Marth 1987; Reitz et al. 1996; Savolainen et al. 1977; Stewart et al. 1970). The distribution of tetrachloroethylene has also been studied in rats and dogs following oral exposure (Dallas

et al. 1994a, 1995). Studies using human subjects indicate increases in the body burden with repeated daily exposure (Altmann et al. 1990; Guberan and Fernandez 1974; Stewart et al. 1970). No other studies are available that correlate duration of exposure with the distribution kinetics. Animal data support predictions from PBPK models that tetrachloroethylene is primarily distributed to, and accumulated in, adipose tissue, the brain, and the liver (Green et al. 1990; Marth 1987; Savolainen et al. 1977; Stewart et al. 1970). Animal studies also indicate that tetrachloroethylene crosses the placenta and is distributed to the amniotic fluid and fetus (Ghantous et al. 1986). A study by Byczkowski and Fisher (1994) indicated that tetrachloroethylene does cross into milk in rats exposed to tetrachloroethylene. Models have been developed to estimate the levels of tetrachloroethylene in breast milk of women exposed to tetrachloroethylene (Byczkowski and Fisher 1994, 1995; Schreiber 1993). Additional studies that determine blood-milk transfer coefficients would be useful for risk assessment. Distribution data following oral and dermal exposure of animals would also be useful, as the potential exists for both oral and dermal exposure of humans in the vicinity of hazardous waste sites.

Human and animal data are available on metabolism following oral exposures (Birner et al. 1996; Buben and O'Flaherty 1985; Dallas et al. 1994a; Dekant et al. 1986; Frantz and Watanabe 1983; Green et al. 1990; Pegg et al. 1979) and inhalation exposures (Birner et al. 1996; Dallas et al. 1994c; Gearhart et al. 1993; Ikeda et al. 1972; Imbriani et al. 1988; Jang et al. 1993; Monster 1986; Monster et al. 1983; Odum et al. 1988; Ogata et al. 1971; Ohtsuki et al. 1983; Pegg et al. 1979; Popp et al. 1992; Reitz et al. 1996; Schumann et al. 1980; Seiji et al. 1989; Skender et al. 1991; Yllner 1961), but not following dermal exposures. One human study indicates that the metabolism of tetrachloroethylene is saturable following inhalation exposure (Ohtsuki et al. 1983). A similar saturation pattern has been observed in both mice and rats following oral exposure. Differences in the metabolites of animals and humans have been seen for inhalation exposures (Bois et al. 1990; Hattis et al. 1990; Odum et al. 1988) and oral exposures (Dallas et al. 1994a, 1995; Dekant et al. 1986). Further studies investigating possible differences according to gender, ethnic population group, or nutritional status, and the effects of enzyme induction on the metabolic rate would also be useful. Research to determine if trichloroethanol is a metabolite of tetrachloroethylene, or is produced from trichloroethylene (a contaminant of tetrachloroethylene), would also be useful. There are no data available regarding the route of exposure as a factor in the relative rates of metabolism.

There are one oral study (Koppel et al. 1985), one dermal study (Stewart and Dodd 1964), and several inhalation studies (Ikeda et al. 1972; Monster et al. 1979; Ogata et al. 1971; Ohtsuki et al. 1983; Opdam and Smolders 1986) on excretion of tetrachloroethylene by humans. The oral data are presumed to be

atypical because the patient was hyperventilated to facilitate pulmonary excretion following an accidental ingestion of the chemical. These human studies indicate that a large percentage of tetrachloroethylene is excreted unchanged in exhaled air (Ohtsuki et al. 1983), with urinary excretion comprising a much smaller percentage (approximately 2%) of the estimated absorbed dose (Ogata et al. 1971). The excretion of the urinary metabolites increased linearly with tetrachloroethylene concentrations, but reached a plateau when the metabolic capacity was saturated (Ikeda et al. 1972). Similar saturation excretion patterns were seen in rats (Pegg et al. 1979). As in inhalation exposure, the majority of unmetabolized tetrachloroethylene administered orally to humans and animals was eliminated via the lungs, with smaller amounts detected in the urine. The elimination of tetrachloroethylene is well characterized; therefore, further studies are not needed at this time.

Uncertainty in the degree of glutathione-mediated metabolism of tetrachloroethylene in humans, and the interindividual variability in this pathway, represents a significant data gap.

Comparative Toxicokinetics. Data are available on the pharmacokinetics of this chemical for different species. Human data (Hake and Stewart 1977; Monster et al. 1979; Opdam and Smolders 1986; Pezzagno et al. 1988; Stewart et al. 1977) and data from rats (Dallas et al. 1994c; Pegg et al. 1979), mice (Schumann et al. 1980), and dogs (Dallas et al. 1994a, 1995) regarding absorption of tetrachloroethylene following inhalation and oral exposure are similar. Distribution following inhalation has not been studied thoroughly in humans, although pharmacokinetic models have been developed. These models and animal data suggest that tetrachloroethylene accumulates mainly in fat (Green et al. 1990; Guberan and Fernandez 1974; Marth 1987; Monster 1986; Savolainen et al. 1977; Stewart et al. 1970). Both animal and human data suggest that the primary target organs are the central nervous system (Rao et al. 1993; Savolainen et al. 1977; Stewart et al. 1970, 1981), the liver (Marth 1987), and the kidney (Franchini et al. 1983; Green et al. 1990; Mutti et al. 1992).

There are differences in the metabolism of tetrachloroethylene in humans and animals. Oxalic acid is an important metabolite in rats (Pegg et al. 1979), but it has not been reported in humans. The metabolism of tetrachloroethylene is known to be saturable in humans (Ohtsuki et al. 1983) and animals (Pegg et al. 1979; Schumann et al. 1980). No human or animal data were located regarding the metabolism of tetrachloroethylene following dermal exposure. In humans, exhalation of unchanged tetrachloroethylene following inhalation (Ikeda et al. 1972; Ogata et al. 1971; Ohtsuki et al. 1983), oral (Koppel et al. 1985), or dermal (Stewart and Dodd 1964) exposure was the primary route of excretion. Because there are differences in the metabolic pattern between humans and rodents, it may be useful to conduct studies

using additional animal models (e.g., primates) so that a metabolic pattern more closely resembling that of humans can be studied. There are also differences in the metabolic patterns of rats and mice (Dekant et al. 1986; Green et al. 1990; Odum et al. 1988). Peroxisome proliferation in the mouse liver has not been shown to have a parallel in the rat kidney, suggesting that the mechanisms of carcinogenicity differ in these two species (Goldsworthy and Popp 1987; Odum et al. 1988). The peroxisome proliferation response in humans is also minimal (Bentley et al. 1993), and the liver effects observed in mice may not occur in humans by the same mechanism. Additional pharmacokinetic data in different species, especially regarding the dynamics of the nervous system distribution of tetrachloroethylene, would be useful to improve PBPK analysis.

Methods for Reducing Toxic Effects. The general recommendations for reducing the absorption of tetrachloroethylene following acute inhalation, oral (HSDB 2013; Stutz and Ulin 1992), dermal (HSDB 2013; Stutz and Ulin 1992), or ocular (Bronstein and Currance 1988; Haddad and Winchester 1990; HSDB 2013; Stutz and Ulin 1992) exposure are well established and have a proven efficacy. No additional investigations are considered necessary at this time.

No clinical treatments other than supportive measures are currently available to enhance elimination of tetrachloroethylene following exposure. Studies designed to assess the potential risks or benefits of increasing ventilation to enhance pulmonary elimination or of stimulating enzymatic pathways to increase the metabolism of tetrachloroethylene could prove useful. However, it should be emphasized that once exposure has ended, the body does not retain significant amounts of tetrachloroethylene for long periods.

The development of treatment protocols designed to interfere with the mechanism of tetrachloroethylene-induced toxic effects would require a sizable research effort. Since the body does not retain significant amounts of tetrachloroethylene for long periods, the relative merits of such an undertaking are not clear. Nevertheless, there is substantive evidence from well-conducted studies suggesting possible methods that could be exploited to block the mode of action that causes neurotoxicity, nephrotoxicity, and hepatotoxicity.

The mechanism of action of tetrachloroethylene for the central nervous system has not been clearly established. However, there are data indicating that the induced neurotoxicity may be related to solvent effects on lipid and fatty acid compositions of membranes (Kyrklund et al. 1984, 1988, 1990). Effects on neurotransmitter systems have also been demonstrated (Korpela and Tahti 1986; Mutti and Franchini

1987). It is reasonable to speculate, therefore, that these effects on neurotransmitters could be mitigated by pharmacologic intervention; however, no such interventions are currently available for clinical use.

The mechanism of action associated with kidney toxicity and nephrocarcinogenicity may involve the formation of reactive intermediates from glutathione conjugates (Dekant et al. 1986, 1987; Green et al. 1990; Henschler 1977). Although evidence from an *in vitro* study of human liver tissue suggests that glutathione conjugation is not important in human biotransformation of tetrachloroethylene (Green et al. 1990), the results are not conclusive. Methods for reducing the destructive damage caused by these intermediates or for blocking their formation through inhibition of β-lyase (Dekant et al. 1986, 1987; Green et al. 1990) may prove effective in reducing kidney toxicity, but are not currently available for clinical use.

One mechanism of action of liver toxicity suggested in the literature is the induction of peroxisome proliferation (and resulting increases in hydrogen peroxide and oxidative damage) by trichloroacetic acid, a metabolite of tetrachloroethylene (Odum et al. 1988). Shifting metabolism away from formation of trichloroacetic acid could theoretically reduce toxicity that might be caused via this mechanism. However, the net effect on all forms of toxicity of tetrachloroethylene by such an alteration in metabolism would need to be carefully evaluated.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Additional human and animal studies are needed to assess whether infants and children are more susceptible than adults to tetrachloroethylene toxicity.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies funded by the National Institutes of Health (NIH) and pertaining to tetrachloroethylene are shown in Table 3-9.

Table 3-9. Ongoing Studies on Tetrachloroethylene

Principal Investigator	Study topic	Institution	Sponsor
Aschengrau, AA	Tetrachloroethylene in the drinking water and risk of birth defects in a population-based case-control study	Boston University Medical Campus, Boston, Massachusetts	National Institute of Environmental Health Sciences
Ozonoff, DM	Epidemiologic studies of neurodevelopment in a population exposed to tetrachloroethylene in the drinking water	Boston University Medical Campus, Boston, Massachusetts	National Institute of Environmental Health Sciences
DeRoos, AJ	Risk of multiple myeloma from exposure to occupational solvents, including tetrachloroethylene	Drexel University, Philadelphia, Pennsylvania	National Institute of Environmental Health Sciences

Source: RePORTER 2013

4. CHEMICAL AND PHYSICAL INFORMATION

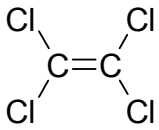
4.1 CHEMICAL IDENTITY

The chemical identity of tetrachloroethylene is shown in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of tetrachloroethylene are shown in Table 4-2.

Table 4-1. Chemical Identity of Tetrachloroethylene

Characteristic	Information	Reference
Chemical name	Tetrachloroethylene	HSDB 2013
Synonym(s)	Ethylene tetrachloride; per; PERC; perchlor; perchloroethylene; perk; 1,1,2,2-tetrachloroethylene; tetrachloroethene; tetrachloroethylene; PCE	HSDB 2013; NIOSH 2013
Registered trade name(s)	Ankilostin; Antisal 1; Dee-Solve; Didakene; Dow-per; ENT 1860; Fedal-Un; Nema; Perclene; Percosolv; Perklone; PerSec; Tetlen; Tetracap; Tetraleno; Tetravec; Tetroguer; Tetropil; Perawin; Tetralex; Dowclene EC	OHM/TADS 1990
Chemical formula	C_2Cl_4	HSDB 2013
Chemical structure		HSDB 2013
Identification numbers:		
CAS registry	127-18-4	HSDB 2013
NIOSH RTECS	kx3850000	HSDB 2013
EPA hazardous waste	U210	HSDB 2013
OHM/TADS	7216847	OHM/TADS 1990
DOT/UN/NA/IMDG shipping	UN1897; IMO 6.1	HSDB 2013
HSDB	49 403 55	HSDB 2013
NCI	NCI-C04580	HSDB 2013

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Tetrachloroethylene

Property	Information	Reference
Molecular weight	165.83	Lide 2008
Color	Colorless	HSDB 2013
Physical state	Liquid (at room temperature)	HSDB 2013
Melting point	-22.3°C	Lide 2008
Boiling point	121.3°C	Lide 2008
Density at 20 °C	1.6230 g/mL	Lide 2008
Odor	Ethereal	HSDB 2013
Odor threshold:		
Water	0.3 ppm	EPA 1987b
Air	1.0 ppm	EPA 1987b
Solubility:		
Water at 25 °C	206 mg/L	HSDB 2013
Organic solvents	Miscible with alcohol, ether, chloroform, benzene, solvent hexane, and most of the fixed and volatile oils	HSDB 2013
Partition coefficients:		
Log K_{ow}	3.40	HSDB 2013
Log K_{oc}	2.2–2.54	Friesel et al. 1984; Seip et al. 1986;
Vapor pressure at 20 °C	18.5 mmHg	HSDB 2013
Henry's law constant at 25 °C	$1.8x10^{-2}$ atm-m^3/mol	Gossett 1987
Autoignition temperature	No data	
Flashpoint	None	HSDB 2013
Flammability limits	Nonflammable	HSDB 2013
Conversion factors	1 mg/L = 147.4 ppm; 1 ppm = 6.78 mg/m^3	HSDB 2013
Explosive limits	No data	

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Tetrachloroethylene is a commercially important chlorinated hydrocarbon solvent and chemical intermediate. It is used as a dry cleaning and textile-processing solvent and for vapor degreasing in metal-cleaning operations. Tetrachloroethylene was first commercially produced in the United States in 1925 via a four-step process using acetylene and chlorine as raw materials (IARC 1979). By 1975, only one U.S. plant was using this process because of the high cost of acetylene.

Currently, the majority of tetrachloroethylene produced in the United States is made by one of three processes: direct chlorination of certain hydrocarbons, chlorination of ethylene dichloride, and oxychlorination. The first process involves the reaction of chlorine with a hydrocarbon such as methane, ethane, propane, or propylene at high temperatures, with or without a catalyst. A chlorinated derivative of a hydrocarbon may also be used. The reaction forms a crude product, which can be purified to yield a marketable grade of tetrachloroethylene. This is easier and more economical than the acetylene process. In addition, the hydrocarbon wastes from other processes can subsequently be used as feedstocks for this process. However, large quantities of hydrogen chloride can be produced. The second process, chlorination of ethylene dichloride, involves noncatalytic chlorination of ethylene dichloride or other C2 chlorinated hydrocarbons. The third process, oxychlorination of ethylene via ethylene dichloride, is widely used to coproduce trichloroethylene and tetrachloroethylene without any net production of hydrogen chloride (Chemical Products Synopsis 1985; Keil 1985; Hickman 2000).

In 1993, the manufacture of tetrachloroethylene via reaction of a hydrocarbon having three or less carbon atoms with a partially chlorinated hydrocarbon, chlorine gas, and carbon tetrachloride at 500–700°C was proposed in a patent. The introduction of carbon tetrachloride to the reaction in a closed system (as opposed to it being formed in the reaction) was to monitor and prevent carbon tetrachloride production in the manufacturing of tetrachloroethylene (Hoshino et al. 1993).

Tetrachloroethylene is produced in the following grades: purified, technical, U.S. Pharmacopoeial (USP), spectrophotometric, and dry cleaning (ACGIH 1991). The dry cleaning and technical grades meet specifications for technical grade, differing only in the amount of stabilizer added to prevent decomposition. Stabilizers, which include amines or mixtures of epoxides and esters, are added to prevent decomposition. Tetrachloroethylene, which is thus stabilized and not easily hydrolyzed, is transported in tanks and drums (ACGIH 1991).

Historical U.S. production volumes of tetrachloroethylene have been reported as follows (C&EN 1994): 547 million pounds in 1983 and 271 million pounds in 1993, respectively. These data show that there was an overall decline of about 50% between 1983 and 1993. According to the U.S. EPA Inventory Update Reporting for 2006, the total U.S. production volume of tetrachloroethylene was between 500 million and < 1 billion pounds (EPA 2013f). The overall demand for tetrachloroethylene was expected to grow at a rate of approximately 1.5% per year from 2007 to 2011(CMR 2008), but data show that the total annual capacity has decreased. In 2011, the directory of chemical producers in the United States listed three major manufacturers with a total annual capacity of 458 million pounds (SRI 2011).

Some of the facilities that manufactured or processed tetrachloroethylene in 2011 are listed in Table 5-1 (TRI11 2013). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Tetrachloroethylene was reported to be produced naturally by several temperate and subtropical marine macroalgae at the rate of 0.0026–8.2 ng/g fresh weight/hour. These species of algae have also been reported to produce trichloroethylene, usually at greater rates. It should be noted, however, that there are results that show that tetrachloroethylene was not detected in cultures of the same algae when the methods of Abrahamsson et al. (1995) were done in the laboratory (Murphy et al. 2000).

5.2 IMPORT/EXPORT

In 1990, about 75.0 million pounds of tetrachloroethylene were imported into the United States, and in 2012, about 26.5 million pounds were imported in the United States (USITC 2013). Exports from the United States were about 55.1 million pounds in 1990 and about 83.8 million pounds in 2012 (USITC 2013).

5.3 USE

Tetrachloroethylene is commercially important as a chlorinated hydrocarbon solvent and as a chemical intermediate. An estimate of the current end-use pattern for tetrachloroethylene is as follows: 60% for chemical intermediate, 18% for dry cleaning and textile processing, 18% for surface preparation and

Table 5-1. Facilities that Produce, Process, or Use Tetrachloroethylene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	3	1,000	99,999	2, 3, 12
AR	5	1,000	999,999	9, 10, 11, 12
CA	21	0	99,999,999	1, 3, 4, 6, 7, 9, 10, 11, 12
CO	2	10,000	99,999	12, 14
CT	1	10,000	99,999	9
DE	1	10,000	99,999	10
FL	1	10,000	99,999	11
GA	9	1,000	999,999	7, 9, 12, 14
HI	1	1,000	9,999	10
IA	1	100,000	999,999	7, 9
IL	10	100	999,999	7, 9, 10, 11, 12
IN	11	100	9,999,999	1, 2, 7, 9, 10, 12, 13, 14
KS	12	0	999,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14
KY	4	10,000	999,999	1, 3, 6, 9, 12
LA	22	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
MA	5	1,000	99,999	2, 3, 9, 11, 12
MI	4	100	999,999	1, 5, 7, 10, 12
MN	4	10,000	999,999	6, 10, 11, 12
MO	7	100	99,999	7, 9, 11, 12
MS	2	10,000	999,999	7, 10
MT	3	0	99,999	10, 12
NC	2	100,000	999,999	7, 9
ND	1	1,000	9,999	10
NE	2	10,000	99,999	7, 12
NJ	2	10,000	99,999	2, 3, 8, 9, 10, 12
NM	1	10,000	99,999	10
NY	7	100	999,999	2, 4, 9, 10, 12, 14
OH	15	100	9,999,999	2, 3, 7, 9, 11, 12, 14
OK	5	1,000	99,999	6, 10, 11, 12
OR	2	1,000	99,999	10, 12
PA	12	1,000	9,999,999	2, 3, 7, 8, 9, 10, 11, 12
RI	1	100,000	999,999	7, 9
SC	2	10,000	99,999	11, 12
TN	2	100	99,999	2, 3, 6, 9, 10, 12
TX	45	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
UT	3	10,000	999,999	10, 12
VA	1	10,000	99,999	12
VI	1	100,000	999,999	10

Table 5-1. Facilities that Produce, Process, or Use Tetrachloroethylene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WA	6	100	999,999	2, 4, 7, 9, 10, 11, 14
WI	6	10,000	99,999	7, 9, 11, 12
WY	1	100	999	10

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacturing Aid
12. Ancillary/Other Uses
13. Manufacturing Impurity
14. Process Impurity

Source: TRI11 2013 (Data are from 2011)

cleaning, 2% for oil refining catalyst regeneration, and 2% for miscellaneous use (Dow 2008). Beginning in 2020, federal regulations are scheduled to begin eliminating the use of tetrachloroethylene in dry cleaning in urban locations (CMR 2008).

In textile processing, tetrachloroethylene is used as a scouring solvent that removes oils from fabrics after knitting and weaving operations, as a carrier solvent for sizing and desizing, and for fabric finishes and water repellents. Tetrachloroethylene is able to dissolve fats, greases, waxes, and oils without harming natural or human-made fibers. However, because of the growing popularity of wash-and-wear fabrics, improved efficiency of dry cleaning equipment, and increased chemical recycling, the demand for tetrachloroethylene as a dry cleaning solvent has steadily declined (EPA 1995). There are three types of tetrachloroethylene dry cleaners as regulated by the EPA's Clean Air Act: large industrial and commercial dry cleaners; freestanding small dry cleaners; and small dry cleaners in apartment buildings. The EPA has required operators to reduce emissions from dry cleaners and has enforced a final rule on the phase out of tetrachloroethlyene use in dry cleaners that are in residential areas by December 21, 2020 (EPA 2006). Currently, approximately 28,000 U.S. dry cleaners use tetrachloroethylene (EPA 2013g).

Another major use of tetrachloroethylene is as a vapor and liquid degreasing agent. Since tetrachloroethylene dissolves many organic compounds, select inorganic compounds, and high-melting pitches and waxes, it can be used to clean and dry contaminated metal parts and other fabricated materials. It is also used to remove soot from industrial boilers (Verschueren 1983). Tetrachloroethylene was used as an anthelmintic in the treatment of hookworm and some nematode infestations, but it has been replaced by drugs that are less toxic and easier to administer (Budavari 1989; HSDB 2013).

5.4 DISPOSAL

The chemical industry has responded to increased environmental and ecological concerns with efforts to improve recovery and recycling of tetrachloroethylene. One method of disposal involves absorption in vermiculite, dry sand, earth, or a similar material and then burial in a secured sanitary landfill (HSDB 2013). A second method involves incineration after mixing with another combustible fuel. With the latter method, combustion must be complete to prevent the formation of phosgene, and an acid scrubber must be used to remove the haloacids produced. The gas-fired type of incinerator is optimal for the total destruction of tetrachloroethylene (HSDB 2013).

Tetrachloroethylene is also a potential candidate for fluidized bed incineration at 450–980°C, rotary kiln incineration at 820–1,600°C, and liquid injection incineration at 650–1,600°C (HSDB 2013).

Federal regulations prohibit land disposal of various chlorinated solvent materials that may contain tetrachloroethylene. Any solid waste containing tetrachloroethylene must be listed as a hazardous waste unless the waste is shown not to endanger the health of humans or the environment (EPA 1985b, 1988). Destruction and removal efficiency of tetrachloroethylene that is designated as a principal organic hazardous constituent must be 99.99%. Discharge of tetrachloroethylene into U.S. waters requires a permit (WHO 1987). Before implementing land disposal of waste residue, environmental regulatory agencies should be consulted for guidance on acceptable disposal practices (HSDB 2013).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Tetrachloroethylene has been identified in at least 945 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for tetrachloroethylene is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 943 are located within the United States and 2 are located in the Commonwealth of Puerto Rico (not shown).

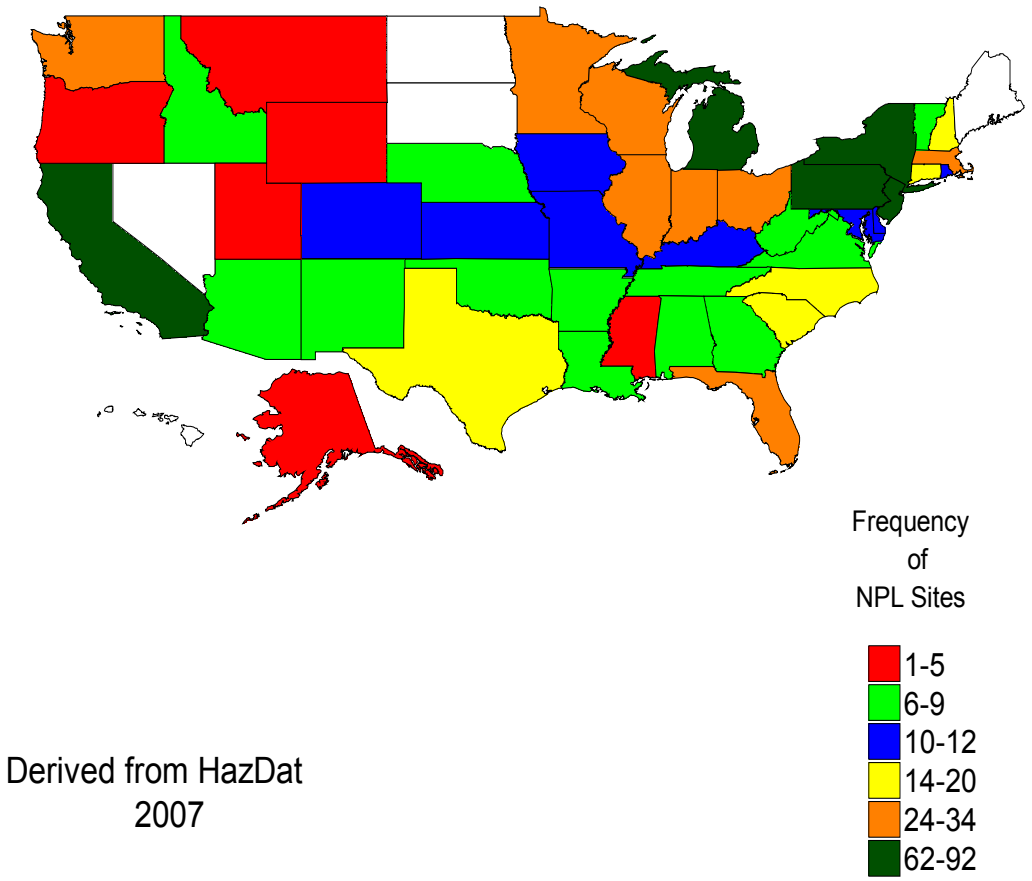
Tetrachloroethylene is a VOC that is widely distributed in the environment. It is released to the environment via industrial emissions and from building and consumer products. Releases are primarily to the atmosphere. However, the compound is also released to surface water and land in sewage sludges and in other liquid and solid waste, where its high vapor pressure and Henry's law constant usually result in its rapid volatilization to the atmosphere. Tetrachloroethylene has relatively low solubility in water and has medium-to-high mobility in soil; thus, its residence time in surface environments is not expected to be more than a few days. However, it persists in the atmosphere for several months and can last for decades in the groundwater.

Tetrachloroethylene is a common dense nonaqeuous phase liquid (DNAPL) that can migrate through the subsurface of water (ITRC 2003). As a result, tetrachloroethylene can also be persistent in the water because it has a higher density than water and relatively low water solubility. Vapor-phase tetrachloroethylene can also seep into the air of homes and commercial buildings from subsurface groundwater and soils through a process called vapor intrusion. Soil vapor, or the air found between soil particles, can become contaminated and migrate up through the soil to the buildings through cracks or perforations in the foundation of the building and in some cases, basement floors or walls. This migration occurs because of pressure differences inside and below the building (NYSDH 2006) and diffusion (EPA 2012m). Because of its pervasiveness and ability to persist under certain conditions, the potential for human exposure may be substantial.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) is an annual compilation of information on the release of toxic chemicals by manufacturing and processing facilities. TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing

Figure 6-1. Frequency of NPL Sites with Tetrachloroethylene Contamination



and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 708,893 pounds (~321 metric tons) of tetrachloroethylene to the atmosphere from 245 domestic manufacturing and processing facilities in 2011, accounted for about 62% of the estimated total environmental releases from facilities required to report to the TRI (TRI11 2013). These releases are summarized in Table 6-1.

Likewise, EPA's National Emission Inventory (NEI) database contains data regarding sources that emit criteria air pollutants and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands (prior to 1999, criteria pollutant emission estimates were maintained in the National Emission Trends [NET] database and HAP emission estimates were maintained in the National Toxics Inventory [NTI] database). The NEI database derives emission data from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Data downloaded from the 2008 NEI indicated that the total emission of tetrachloroethylene was approximately 5,361 tons, with the biggest source arising from its use as a dry cleaning solvent (EPA 2013b). These data are summarized in Table 6-2.

Environmental releases of tetrachloroethylene also occur at sites of its manufacture and at sites of production of other chlorohydrocarbons (such as ethylene dichloride and methylene chloride) in which tetrachloroethylene is formed as a byproduct (Weant and McCormick 1984). Tetrachloroethylene

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Tetrachloroethylene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	3	6,567	0	0	0	0	6,567	0	6,567
AR	5	22,486	0	0	0	92,138	22,486	92,138	114,624
CA	21	87,103	1	0	1,835	0	88,938	1	88,939
CO	2	0	0	0	0	800	0	800	800
CT	1	22	0	0	0	0	22	0	22
DE	1	10	0	0	0	0	10	0	10
FL	1	20,583	0	0	1,100	0	20,583	1,100	21,683
GA	9	14,526	0	0	3	6,977	14,526	6,980	21,506
HI	1	0	0	0	0	0	0	0	0
IA	1	0	0	0	0	0	0	0	0
IL	10	15,415	5	0	14	0	15,425	9	15,434
IN	11	27,900	0	0	0	0	27,900	0	27,900
KS	12	163,419	0	3,559	2,152	0	166,978	2,152	169,130
KY	4	6,887	0	0	36,162	0	6,887	36,162	43,049
LA	22	110,505	148	0	153	0	110,653	153	110,806
MA	5	14,122	0	0	0	0	14,122	0	14,122
MI	3	11,216	24	0	22,638	0	33,569	309	33,878
MN	4	2,504	9	0	10	0	2,513	10	2,523
MO	7	27,753	0	0	0	0	27,753	0	27,753
MS	2	1,358	0	0	0	0	1,358	0	1,358
MT	3	1,554	0	0	25	0	1,578	1	1,578
NC	2	3,858	0	0	0	45,328	3,858	45,328	49,186
ND	1	490	0	0	0	0	490	0	490
NE	2	11,642	0	0	0	0	11,642	0	11,642
NJ	2	173	0	0	0	64	173	64	237
NM	1	18	0	0	0	0	18	0	18
NY	7	19,756	38	0	0	17,165	19,794	17,165	36,959
OH	15	14,203	5	35,879	1,888	7,245	50,087	9,133	59,220
OK	5	6,000	0	0	5	1,050	6,005	1,050	7,055
OR	2	11,404	0	0	85,349	0	96,726	27	96,753
PA	12	26,973	7	0	505	30,943	26,980	31,448	58,428
RI	1	551	0	0	0	0	551	0	551
SC	2	1,942	0	0	15	550	1,942	565	2,507
TN	2	822	0	0	0	0	822	0	822
TX	45	67,309	79	43,485	590	499	110,903	1,059	111,962
UT	3	200	5	0	0	0	205	0	205

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Tetrachloroethylene[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
VA	1	3,491	0	0	0	0	3,491	0	3,491
VI	1	153	0	0	0	0	153	0	153
WA	6	656	1	0	1	385	658	385	1,043
WI	6	5,317	0	0	0	0	5,317	0	5,317
WY	1	5	0	0	0	0	5	0	5
Total	245	708,893	323	82,923	152,444	203,144	901,688	246,039	1,147,726

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI11 2013 (Data are from 2011)

Table 6-2. Emissions of Tetrachloroethylene

Emission sector	Emissions (pounds)
Bulk gasoline terminals	3,394.73
Commercial cooking	0
Dust; construction dust	56.05
Fuel comb; commercial /institutional, biomass	1,132.58
Fuel comb; commercial /institutional, coal	36.20
Fuel comb; commercial /institutional, natural gas	10,681.70
Fuel comb; commercial /institutional, oil	301.86
Fuel comb; commercial /institutional, other	599.15
Fuel comb; electric generation, biomass	2,691.08
Fuel comb; electric generation, coal	41,672.06
Fuel comb; electric generation, natural gas	545.02
Fuel comb; electric generation, oil	71.07
Fuel comb; electric generation, other	2,646.36
Fuel comb; industrial boilers, ICEs, biomass	15,337.23
Fuel comb; industrial boilers, ICEs, coal	1,386.21
Fuel comb; industrial boilers, ICEs, natural gas	2,377.53
Fuel comb; industrial boilers, ICEs, oil	16,159.03
Fuel comb; industrial boilers, ICEs, other	827.79
Fuel comb; residential, natural gas	0
Fuel comb; residential, oil	0
Fuel comb; residential, other	12.26
Gas stations	49.97
Industrial processes; cement manufacturing	46.34
Industrial processes; chemical manufacturing	70,789.19
Industrial processes; ferrous metals	5.60
Industrial processes; mining	0.54
Industrial processes; NEC	144,943.85
Industrial processes; non-ferrous metals	87,002.84
Industrial processes; oil and gas production	1,140.31
Industrial processes; petroleum refineries	24,768.85
Industrial processes; pulp and paper	126,152.51
Industrial processes; storage and transfer	80,568.03
Miscellaneous non-industrial NEC	0
Mobile; non-road equipment, diesel	1,100.80
Solvent; consumer and commercial solvent use	911,059.81
Solvent; degreasing	1,236,680.40
Solvent; dry cleaning	7,471,498.64
Solvent; graphic arts	4,792.01
Solvent; industrial surface coating and solvent use	820,254.87

Table 6-2. Emissions of Tetrachloroethylene

Emission sector	Emissions (pounds)
Solvent; non-industrial surface coating	162,519.17
Waste disposal	477,429.76

ICE = internal combustion engine; NEC = not elsewhere classified

Source: EPA (2013b).

emissions to the atmosphere may occur at sites used in disposing the chemical (EPA 2013b, TRI11 2013), including incineration facilities for municipal and hazardous waste (Oppelt 1987). Tetrachloroethylene is also speculated to be released to the atmosphere from the ocean where it is produced by some macroalgae (Abrahamsson et al. 1995).

Tetrachloroethylene partitions primarily to the atomosphere when released into the environment (NICNAS 2001). The highest levels of tetrachloroethylene emissions from the dry cleaning industry are from uncontrolled, or fugitive, emissions (OSHA 2005). In addition, due to its volatility, tetrachloroethylene lost from contaminated soil can escape to the atmosphere (LHWMP 2013).

Vapor-phase tetrachloroethylene can migrate into the air of homes and buildings from below a contaminated site. For example, through the process known as vapor intrusion, tetrachloroethylene was found to leach into the soil to the aquifer from improper storage of the chemical in a Colorado building. The vapors from contaminated groundwater and/or soils were found to migrate through the vadose zone, and then into homes and buildings (Agency for Toxic Substances and Disease Registry 2006).

The concept of vapor intrusion was introduced in the late 1990's. It was previously thought that contaminated water was a threat only when the groundwater was used as drinking water. In 1979, 4,100 gallons of 1,1,1-trichloroethlyene were spilled in the Village of Endicott, New York. Tetrachloroethylene was one of the many chemicals found in the groundwater analysis after the spill; however, the compound was not present because of the spill, but rather from previous spills amd releases. In 2000–2001, it was discovered that residents in the Village of Endicott, New York, were exposed to 0.1–24 $\mu g/m^3$ of tetrachloroethylene in the indoor air. The reference limit for tetrachloroethylene is 2.2 $\mu g/m^3$ (Forand et al. 2012). McDonald and Wertz (2007) proposed that such high concentrations of tetrachloroethylene were primarily due to background sources of tetrachloroethylene rather than vapor intrusion processes.

Tetrachloroethylene has been detected in several other sites as indicated in the Environmental Protection Agency's Vapor Intrusion Database (EPA 2012l). In Texas, the indoor air in homes of communities that sit above groundwater contaminated with tetrachloroethylene were analyzed. It was found that concentrations of tetrachloroethylene increased with the magnitude of the barometric pressure drop, humidity, and groundwater concentrations due to vapor intrusion. Concentrations of tetrachloroethylene decreased when wind speed increased, during winter, and in homes without air conditioners (Johnston and Gibson 2013).

Similarily, spatial locations and temporal changes are important factors when assessing sites contaminated with tetrachloroethylene. Spatial and temporal variability can lead to variations in the vapor intrusion process. In other words, it may be difficult to assess the impact of tetrachloroethylene above ground because factors such as the season of year, time of month, space between homes, etc. may alter the concentrations below ground. In some cases, the presence of contamination below ground does not always lead to contaminated vapors above ground (Folkes et al. 2009).

Alternatively, Pennell et al. (2013) found that there were higher levels of tetrachloroethylene on the first floor of homes, with lower levels of tetrachloroethylene in the basement of homes at a research site in Boston. These higher levels on the first floor were accompanied by sewer gas smells. The authors reported that tetrachloroethylene can be present in sewer gas from bathroom plumbing that, in turn, can contaminate indoor air as well.

6.2.2 Water

Estimated releases of 323 pounds of tetrachloroethylene to surface water from 245 domestic manufacturing and processing facilities in 2011, accounted for about 0.03% of the estimated total environmental releases from facilities required to report to the TRI (TRI11 2013). These releases are summarized in Table 6-1.

A variety of industries that use tetrachloroethylene (such as metal degreasing and dry cleaning) generate aqueous wastes containing the compound, which subsequently end up at waste treatment facilities (Weant and McCormick 1984). Aeration processes at waste treatment facilities strip much of the tetrachloro-ethylene from the water and release it into the atmosphere as a result of the high volatility of this chemical (Lurker et al. 1982). Exchange rates of tetrachloroethylene from water to air were measured by means of the Reynolds number. Tetrachloroethylene had exchange rates of 3.13–82.0 as a function of the VOCs in the water and oxygen in the atmosphere (DeWulf et al. 1998).

Tetrachloroethylene has also been detected in groundwater due to inappropriate disposal and release from dry cleaning facilities or landfills in Canada and the United States. Tetrachloroethylene has been detected in most drinking water, groundwater, surface water and rainwater supplies. Tap water may be an important source of exposure to tetrachloroethylene when levels of the compound are >10 ppb in the water supply (CEPA 2001). Three percent of the water supply systems that use well water contain

≥0.5 µg/L tetrachloroethylene (WHO 2003). One of the primary causes of contamination was found to be due to solvent degreasing activities. Tetrachloroethylene volatilizes readily into the atmosphere due to the high volatility of the compound; however, it can also persist in the groundwater for decades (CDPHE 2002). Concentrations of tetrachloroethylene in the groundwater are not expected to be at levels that heavily impact aquatic life (NICNAS 2001).

In addition to industrial releases, tetrachloroethylene can be released in the drinking water by leaching into the water from liners in pipes, as in the case of contaminated water in New England. The liners were installed to asbestos cement pipes to take away a foul taste in the water (Larson et al. 1983). They were comprised of vinyl plastic and tetrachloroethylene. The manufacturers expected tetrachloroethylene to volatilize from the pipe after they administered the compound; however, it stayed in the coating and was found to progressively leach into the drinking water (Aschengrau et al. 2003). Tetrachloroethylene was present at concentrations ranging from 1.5 to 7,750 µg/L in Cape Cod, Massachusetts, and was reduced to 40 µg/L after bleeding and flushing the pipes (Aschengrau et al. 2012).

6.2.3 Soil

Estimated releases of 152,444 pounds (~69 metric tons) of tetrachloroethylene to soils from 245 domestic manufacturing and processing facilities in 2011, accounted for about 13% of the estimated total environmental releases from facilities required to report to the TRI (TRI11 2013). An additional 82,923 pounds (~37 metric tons), constituting about 7% of the total environmental emissions, were released via underground injection (TRI11 2013). These releases are summarized in Table 6-1.

Many of the processes in which tetrachloroethylene is used as a solvent involve recycling the compound by various methods (EPA 1991a). These recycling methods produce tetrachloroethylene-containing sludges and dirty filters that have been landfilled in the past. Contamination of soil can occur through leaching of tetrachloroethylene from these disposal sites (NICNAS 2001; Schultz and Kjeldsen 1986). Leaking of tetrachloroethylene from underground storage tanks can also result in the contamination of soil. When released to the soil, tetrachloroethylene may be evaporated into the atmosphere or leach into the groundwater (Newcombe 2000). Tetrachloroethylene can enter the subsurface groundwater as a DNAPL, migrate to the surface waters, and enter in homes and buildings (ITRC 2003).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

The predicted degradation half-life of tetrachloroethylene in the atmosphere indicates that long-range global transport is likely (Class and Ballschmiter 1986). Indeed, monitoring data have demonstrated that tetrachloroethylene is present in the atmosphere worldwide and at locations far removed from anthropogenic emission sources (see Section 6.4.1).

Tetrachloroethylene has been detected in a number of rainwater samples collected in the United States and elsewhere (see Section 6.4.2). However, the relatively low water solubility of tetrachloroethylene suggests that wet deposition as a result of scavenging by rainwater occurs very slowly compared to other volatile chlorinated hydrocarbons. For example, concentrations of the more water soluble 1,1,1-trichloroethane fell to below detection limits during a 12-hour rain event, while concentrations of tetrachloroethylene fell only slightly during the same time period (Jung et al. 1992). Dry deposition does not appear to be a significant removal process (Cupitt 1987), although substantial evaporation from dry surfaces can be predicted from the high vapor pressure.

Laboratory studies have demonstrated that tetrachloroethylene volatilizes rapidly from water (Chodola et al. 1989; Dilling 1977; Dilling et al. 1975; Okouchi 1986; Roberts and Dandliker 1983; Zytner et al. 1989b). One study found that only 2.7% of the initial mass of tetrachloroethylene remained in stagnant water with a surface-to-volume ratio of 81 m^2/m^3 after 4.5 hours (Zytner et al. 1989b). Dilling et al. (1975) reported the experimental half-life with respect to volatilization of 1 mg/L tetrachloroethylene from water to be an average of 26 minutes at approximately 2°C in an open container. This behavior is consistent with its high Henry's law constant and first-order kinetics. Other factors that influence volatilization rates are ambient temperature, water movement and depth, associated air movement, and surface-to-volume ratio. In laboratory models using beakers of stagnant water, the rate of tetrachloroethylene volatilization was found to increase with increasing surface-to-volume ratio (Chodola et al. 1989; Zytner et al. 1989b). Data from these models also demonstrated that volatilization from water was independent of concentration.

The volatilization half-life of tetrachloroethylene from a rapidly moving, shallow river (1 m deep, flowing 1 m/second with a wind velocity of 3 m/second) has been estimated to be 4.2 hours (Thomas 1982). Measured volatilization half-lives in a mesocosm, which simulated the Narragansett Bay in Rhode Island during winter, spring, and summer, ranged from 12 days in winter conditions to 25 days in spring

conditions (Wakeham et al. 1983). Measurements of tetrachloroethylene levels in Lake Zurich, Switzerland, indicated that volatilization is the dominant removal process in surface waters (Schwarzenbach et al. 1979).

Laboratory studies modeling soil systems have demonstrated that volatilization rates for tetrachloroethylene from soil are much less than those from water (Park et al. 1988; Zytner et al. 1989b). Volatilization rates from soil, like water, appear to be related to surface-to-volume ratio (Zytner et al. 1989b). However, the authors of these studies also found a direct relationship between the concentration of the chemical in soil and rate of volatilization, which contrasts with results seen in water, probably because concentration gradients are a more significant factor in soils than in uniformly mixed water (Zytner et al. 1989b). Soil type also influenced the volatilization rate in this study, with the rate in a high organic carbon top soil greatly reduced compared to that of a low organic carbon, sandy loam. Contrasting results were seen in another study, which found that soil type had no effect on rate of volatilization (Park et al. 1988). However, this may simply be a reflection of the fact that the differences between soils used in this study, particularly organic carbon content, were not very great. Park et al. (1988) found that 20% of the applied tetrachloroethylene was volatilized 168 hours after treatment. In general, it can be said that losses of tetrachloroethylene from soil resulting from volatilization seem to be between 10- and 100-fold slower than from water, depending on soil type, which directly affects the amount of sorption (Park et al. 1988; Zytner et al. 1989b).

Sorption of chlorinated solvents is expected to be a function of the organic carbon content in sediments and soils. Experimentally measured soil sorption coefficients based on the organic carbon content (K_{oc}) ranged from 646 to 6,026. The values were collected from three Danish contaminated clayey till sites. Each site had differing clay contents ranging from 23.0 to 27.0% clay (Lu et al. 2011). These values are indicative of low mobility in the soil. Older experimental measured K_{oc} values for tetrachloroethylene ranged from 177 to 534 (Seip et al. 1986). These values are indicative of medium-to-high mobility in soil (Kenaga 1980; Swann et al. 1983). Others have also shown that tetrachloroethylene is highly mobile in sandy soil (Wilson et al. 1981). Another study comparing predicted and observed sorption on clay and organic soils suggested that sorption/desorption to inorganic mineral surfaces may also play a role, and the reactions generally follow reversible pseudo first-order kinetics (Doust and Huang 1992). The movement of tetrachloroethylene in soil has been confirmed by band-infiltration systems in the Netherlands, where tetrachloroethylene has been reported to leach rapidly into groundwater (Piet et al. 1981).

In addition, mobility of tetrachloroethylene in the soil, as well as aqueous solubility, is also enhanced with the presence of humic substances in the surface water or waste water. Effluent concentrations of tetrachloroethylene were found to be much higher with the addition of humic acid in the feed solution. This change in concentration was dependent on the particular chemical, the carbon content, and the presence of humic acid (Diamadopoulos et al. 1998).

Several models for describing the transport of volatile chlorinated hydrocarbons in soils have been developed, often by fitting one or more parameters to experimental data. One model that determined all parameters *a priori* and included transfer between solid, liquid, and gas phases found that the Henry's law constant was the primary determinant of transport behavior in a wet, nonsorbing aggregated medium, suggesting that volatilization and movement in the gas phase accounts for a large portion of tetrachloroethylene movement in soils (Gimmi et al. 1993).

Similarily, exposure pathways, or models, have been developed that help to explain the transport of chemicals, including tetrachloroethylene, into homes through vapor intrusion. Johnson and Ettinger (1991) developed a heuristic model that utilizes equations and several assumptions to estimate the vapor intrusion rate of contaminants. Abreu and Johnson (2005) developed a three-dimensional model that takes in account the relationships between vapor source, building structure, and indoor air impacts. Similarily, Pennell et al. (2009) established a three-dimensional model that also implements advective and diffusive transport. The model was applied to five different scenarios that took into account unique factors such as the building structure, location, and size.

Remediation efforts have been undertaken to facilitate the removal of sorbed and deposited chemicals in the environment as those same chemicals enter the subsurface as a DNAPL, get held by the soil, and leach out of the soil into the groundwater (Pennell et al. 1994). Tetrachloroethylene, however, can be difficult to remediate, and remediation efforts, while aggressive, do not always result in complete restoration. Workshops have been devoted to efforts of understanding remediation efforts in soils contaminated by chlorinated solvents (Stroo et al. 2012).

Soil remediation is usually characterized as either *ex-situ* (out of ground) or *in-situ* (in the ground). *Ex-situ* soil remediation is the more cost-effective technique; it usually involves the moving of the contaminated material to another site for disposal (CDPHE 2006). *In-situ* soil remediation of DNAPLs involves a variety of techniques. One of the more common techniques of *in-situ* soil remediation is soil vapor extraction that includes the formation of wells. The wells are used to bring up vapors trapped in the

subsurface soils by applying negative pressure to the vadose zone (CDPHE 2006). Remediation efforts were undertaken in Saga, Japan, where tetrachloroethylene contaminated sites were cleaned up by soil vapor extraction. Contamination of the site was likely due to tetrachloroethylene being trapped in a surface clay sand layer (vadose zone), gradually diffused into the soil vapor, and dissolved into rainfall and subsequently groundwater (Chia and Miura 2004).

Mobilization of tetrachloroethylene with mixtures of sodium sulfosuccinate (a surfactant) was shown to be the best method for removing residual tetrachloroethylene from Ottawa sand (Pennell et al. 1994). Contaminants in the soil can also undergo remediation by *in-situ* thermal treatment (ISTT); however, this technique is the most costly and often does not eliminate all of the compound. *In-situ* chemical oxidation (ISCO) involves the reaction of oxidation products (hydrogen peroxide, potassium permanganate, etc.) with the contaminant to produce less harmful byproducts; however, this technique is also costly and there have been issues with concentrations of the compounds rebounding after treatment. *In-situ* bioremediation (ISB) facilitates reductive dechlorination by adding electron donors to the soil (Stroo et al. 2012). Reductive dechlorination in tetrachloroethylene involves the reduction of tetrachloroethylne to ethene by removal of the chlorine atoms (CDPHE 2006). Stroo et al. (2012) lists chemical reduction as a natural process that involves degradation of the contaminant.

A considerable number of monitoring studies have detected tetrachloroethylene in groundwater (see Section 6.4.2), which is further evidence of its mobility in soil. Tetrachloroethylene was observed to leach rapidly into groundwater near sewage treatment plants in Switzerland (Schwarzenbach et al. 1983). No evidence of biological transformation of tetrachloroethylene in groundwater was found in this study. Accurate prediction of tetrachloroethylene transport in groundwater is complicated by the sorption effect of organic and inorganic solids (Doust and Huang 1992). Analysis of groundwater in Massachusetts contaminated with tetrachloroethylene indicated that movement of the chemical was not retarded by sorption to sediment (Barber et al. 1988), although this phenomenon may be site specific. Contrasting data from an experiment in a sand aquifer indicated that the movement of tetrachloroethylene through the aquifer was significantly retarded, and the retardation was attributed to sorption (Roberts et al. 1986).

Groundwater remediation techniques range from traditional to innovative. Traditional methods include the use of a groundwater pump-and-treat method and are usually less cost effective. Innovative methods include *in-situ* remediation (enhanced bioremediation, direct chemical oxidation, air sparging, aquifer flushing, and thermal treatment). The innovative techniques usually are cost effective; however, there are

problems when attempting to treat the specific contaminated area with the treatment chemical (CDPHE 2006).

Experimentally measured bioconcentration factors (BCFs), which provide an indication of the tendency of a chemical to partition to the fatty tissue of organisms, have been found to range between 10 and 100 for tetrachloroethylene in fish (Kawasaki 1980; Kenaga 1980; Neely et al. 1974; Veith et al. 1980). Barrows et al. (1980) estimated a BCF of 49 for bluegill sunfish. Somewhat lower BCFs were determined by Saisho et al. (1994) for blue mussel (25.7) and killifish (13.4). Measured bioconcentration factors in Norway spruces were 64.4–85.3 (Polder et al. 1998). These numbers are suggestive of a low tendency to bioconcentrate.

Monitoring data on tetrachloroethylene concentrations in seawater and associated aquatic organisms are in agreement with the experimental BCF data. Concentrations of tetrachloroethylene (dry weight basis) detected in fish (eel, cod, coalfish, dogfish) from the relatively unpolluted Irish Sea ranged from below detection limits to 43 ppb (Dickson and Riley 1976). Levels of 1–41 ppb (wet weight) in liver tissue up to 11 ppb (wet weight) in other tissue were found in various species of fish collected off the coast of Great Britain near several organochlorine plants (Pearson and McConnell 1975). Clams and oysters from Lake Pontchartrain near New Orleans had tetrachloroethylene levels averaging up to 10 ppb (wet weight) (Ferrario et al. 1985).

To assess bioaccumulation in the environment, the level of tetrachloroethylene in the tissues of a wide range of organisms was determined (Pearson and McConnell 1975). Species were chosen to represent several trophic levels in the marine environment. The maximum overall increase in concentration between sea water and the tissues of animals at the top of food chains, such as fish liver, sea bird eggs, and sea seal blubber, was <100-fold for tetrachloroethylene. Biomagnification in the aquatic food chain does not appear to be important (Pearson and McConnell 1975). Bioaccumulation in plants may be indicated by the presence of tetrachloroethylene in fruits and vegetables (see Section 6.4.4), but care must be used in interpreting these studies because it is often unclear whether accumulation took place during growth or at some point after harvesting. Exposure of plants to a contaminant can occur from the roots via the soil or the aboveground plants via the vapors and aerosols in the air. Since plants contribute to human and animal diets, the contaminant levels may contribute significantly to the total daily intake in humans (Polder et al. 1998).

6.3.2 Transformation and Degradation

6.3.2.1 Air

The dominant transformation process for tetrachloroethylene in the atmosphere is a reaction with photochemically produced hydroxyl radicals (Singh et al. 1982). Using the recommended rate constant for this reaction ($1.67x10^{-13}$ cm^3/molecule-second) and a typical atmospheric hydroxyl (OH) radical concentration of $5x10^5$ molecules/cm^3 (Atkinson 1985), the half-life is calculated at about 96 days. Class and Ballschmiter (1986) estimated a half-life of approximately 70 days. An atmospheric lifetime of 119–251 days was calculated by Cupitt (1987), assuming removal by reaction with hydroxyl radicals and using a range of temperatures, rates, and hydroxyl radical concentrations. It should be noted that the half-lives determined by assuming first-order kinetics represent the calculated time for loss of the first 50% of tetrachloroethylene; the time required for the loss of the remaining 50% may not follow first-order kinetics and may be substantially longer.

The reaction of volatile chlorinated hydrocarbons with hydroxyl radicals is temperature-dependent and is thus expected to proceed more rapidly in the summer months. The degradation products of this reaction include phosgene, chloroacetylchlorides, formic acid, carbon monoxide, carbon tetrachloride, and hydrochloric acid (Gay et al. 1976; Itoh et al. 1994; Kirchner et al. 1990; Singh et al. 1975). Reaction of tetrachloroethylene with ozone in the atmosphere is too slow to be an effective agent in tetrachloroethylene removal (Atkinson and Carter 1984; Cupitt 1987).

EPA considers the photochemical reactivity of tetrachloroethylene leading to the production of ambient ozone to be negligible (EPA 1996a). Therefore, tetrachloroethylene has been added to the list of compounds excluded from the definition of volatile organic compounds for purposes of preparing state implementation plans to attain the national ambient air quality standards for ozone.

6.3.2.2 Water

Studies of photolysis and hydrolysis conducted by Chodola et al. (1989) demonstrated that photolysis did not contribute substantially to the transformation of tetrachloroethylene. Chemical hydrolysis appeared to occur only at elevated temperature in a high pH (9.2) environment, and even then, at a very slow rate.

Results from experiments conducted at high pH and temperature were extrapolated to pH 7 and 25°C (Jeffers et al. 1989), and the estimated half-life was $9.9x10^8$ years, which suggests that hydrolysis does

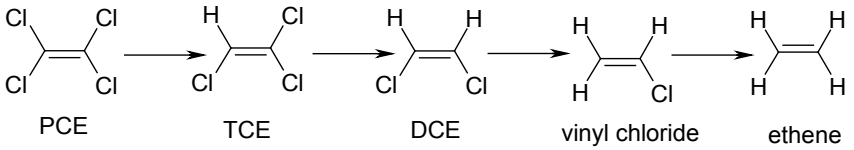
not occur under normal environmental conditions. In contrast, estimates of the hydrolysis half-life of tetrachloroethylene under corresponding conditions were cited in other studies as about 9 months (Dilling et al. 1975) and 6 years (Pearson and McConnell 1975). It is not clear why there is such a large difference between these values; however, errors inherent in the extrapolation method used in the first approach (Jeffers et al. 1989) and the presence of transformation factors other than chemical hydrolysis, such as microbial degradation, in the second approach (Dilling et al. 1975; Pearson and McConnell 1975) may account for the discrepancy in the estimates of half-lives.

Most tetrachloroethylene present in surface waters can be expected to volatilize into the atmosphere. However, tetrachloroethylene is DNAPL and as such, is denser than water and only slightly soluble in water. The tetrachloroethlyene that is not immediately volatilized may be expected to sink and be removed from contact with the surface (Doust and Huang 1992). Volatilization will therefore not be a viable process for this fraction of tetrachloroethylene, which may instead be rapidly transported into groundwater by leaching through fissures rather than matrix pores (Chilton et al. 1990). The sinking of tetrachloroethylene into groundwater also makes cleanup and remediation efforts difficult.

Various aerobic biodegradation screening tests and laboratory studies have shown tetrachloroethylene to be resistant to biotransformation or biodegraded only slowly (Bouwer and McCarty 1982; Bouwer et al. 1981; Wakeham et al. 1983). Newer studies indicate that aerobic degradation of tetrachloroethylene is possible with the white rot fungus, *Trametes versicolor*. The degradation product, tichloroacetic acid, is formed by cytochrome P450-mediated oxidation of tetrachloroethylene (Marco-Urrea et al. 2006).

Anaerobic screening studies have noted more rapid biodegradation, with the presence of microbes that are adapted to tetrachloroethylene (Parsons et al. 1984, 1985; Tabak et al. 1981). Biotransformation is the primary factor in the anaerobic degradation of tetrachloroethylene fromsoil and groundwater pollution.

Anaerobic biodegradation is possible by reductive dechlorination, with the degradation products of tetrachloroethylene being trichloroethylene, cis/trans-dichloroethylene, vinyl chloride, and ethane (see below). Tetrachloroethylene is dehalogenated to trichloroethylene (TCE), trichloroethylene to cis/trans-dichloroethylene (DCE), dichloroethylene to vinyl chloride, and eventually vinyl chloride to ethene. While complete degradation to ethene is possible, traces of vinyl chloride usually remain because of the rate-limiting step from vinyl chloride to ethene.



An anaerobic enrichment culture that degraded 99% of large concentrations of tetrachloroethylene to ethene in the absence of methanogenesis was discovered in 1991 (DiStefano et al. 1991). Tetrachloroethylene was also found to be converted to ethene by a culture containing *Dehalococcoides.* The culture was obtained from a chlorinated ethene anaerobic contaminated aquifer in Bitterfield, Germany. It was found that the microorganisms use tetrachloroethylene and other chlorinated ethenes as electron acceptors with lactate as the electron donor. The reductive dechlorination process also allows for the growth and energy conservation of the microorganisms (Cichocka et al. 2010).

New bacteria are also being discovered from contaminated sites. Tetrachloroethylene is transformed via trichloroethylene to cis-1,2-dichloroethene at high rates with the presence of the aerobic strain MS-1 (Sharma and McCarty 1996). In addition, new and emerging tests, such as isotope fractionation, have proven to be useful in the analysis of the dechlorination of tetrachloroethylene to ethene in contaminated aquifers. With isotope fractionation, a shift in the compound-specific isotope ratios indicates that biodegradation has occurred. The origin or source of the contaminant can also be identified from this shift (Hunkeler et al. 1999).

6.3.2.3 Sediment and Soil

Biodegradation of tetrachloroethylene in soil was thought to occur only under specific conditions, and then only to a limited degree. When subsurface soil samples containing toluene-degrading bacteria were collected from a floodplain in Oklahoma and incubated with tetrachloroethylene, no detectable degradation occurred (Wilson et al. 1983a). However, recent studies have indicated that tetrachloroethylene is able to be degraded under both aerobic and anaerobic conditions.

Tetrachloroethylene was aerobically degraded by *Pseudonomas stutzeri* OX1 with the expression of toluene-o-xylene monoxygenase (Ryoo et al. 2000). Anaerobically, tetrachloroethylene is metabolized by microorganisms through a reductive dechlorination process to trichloroethylene, dichloroethylene, and vinyl chloride, with the major intermediate being trichloroethylene (Vogel and McCarty 1985). In one study, anaerobic enrichment cultures, which support methanogenesis, were found to be capable of dechlorinating tetrachloroethylene to ethylene in the presence of an electron donor (Freedman and Gossett

1989). Recent studies have also indicated that the complete anaerobic degradation of tetrachloroethylene can occur with mixed cultures and sediments (Krumholz et al. 1996).

Cabirol et al. (1996) found that a methanogenic and sulfate-reducing mixed culture from the anaerobic sludge of a waste water treatment plant has the potential to dechlorinate tetrachloroethylene through reductive dechlorination. Tetrachloroethylene was found to have completely disappeared within 37 days and as it disappeared, trichloroethylene was formed. Cabirol et al. (1998) also found that tetrachloroethylene was completely degraded with the same cultures in a fixed bed reactor. In addition, anaerobic biodegradation of very high concentrations of tetrachloroethylene (600 μM) occurred in a continuous flow system in a period of <21 months. Very high concentrations of tetrachloroethylene were completely degraded to vinyl chloride in the 21 months, and vinyl chloride was observed to be degraded to ethene over a longer period of time (Isalou et al. 1998).

Tetrachloroethylene was 94% anaerobically degraded using a mixed enriched culture. Culture enrichment was performed on a sample contaminated with tetrachloroethylene and other halogenated aliphatic compounds obtained from ditch sludge mixed with sewage (Chang et al. 1998). Tetrachloroethylene was also completely degraded to the intermediate 1,2-dichlroethene in 13 days, and subsequently to ethene after 130 days, with a mixed anaerobic culture AMEC-4P (Kim et al. 2010).

In addition, new isolates that degrade tetrachloroethylene are being discovered, such as the strain *Propionibacterium sp.* HK-1, which was able to degrade tetrachloroethylene by 20% (Chang et al. 2011).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to tetrachloroethylene depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of tetrachloroethylene in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. The analytical methods available for monitoring tetrachloroethylene in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Outdoor (ambient) air monitoring studies in the United States have shown tetrachloroethylene concentrations of 400–2,100 ng/m^3 (0.058–0.31 ppb) in Portland, Oregon, in 1984 (Ligocki et al. 1985), 5.2 μg/m^3 (0.77 ppb) in Philadelphia, Pennsylvania, in 1983–1984 (Sullivan et al. 1985), 0.24–0.46 ppb in

three New Jersey cities during the summer of 1981 and the winter of 1982 (Harkov et al. 1984), and 0.29–0.59 ppb in seven cities in 1980–1981 (Singh et al. 1982). A Total Exposure Assessment Methodology (TEAM) study of three industrialized areas detected levels ranging from 0.24 to 9.0 μg/m^3 (0.035–1.33 ppb) (Hartwell et al. 1987). In these studies, levels were found to vary between the fall/winter season and the spring/summer season, with fall/winter levels usually higher. This is consistent with the observation that higher temperatures increase the rate of reaction with hydroxyl radicals and subsequent degradation of tetrachloroethylene (see Section 6.3.2.1).

Tetrachloroethylene was detected at levels ranging from 32 to 75 ng/m^3 (0.0047–0.011 ppb) at five locations in the Antarctic (Zoccolillo et al. 2009). It was also found that there were elevated levels of tetrachloroethylene and other volatile chlorinated hydrocarbons in the winter in Niigata, Japan between April 1989 and March 1992 (Kawata and Fujieda 1993). A rural site in this study had annual mean concentrations between 0.031 and 0.045 ppb, while four industrial sites had mean concentrations between 0.082 and 1.0 ppb.

Data from ambient air monitoring studies in Canada have shown tetrachloroethylene concentrations of 0.03–0.73 ppb in urban locations and 0.03–0.06 ppb in a rural location (CEPA 1993).

The Air Quality System (AQS) database is EPA's repository of criteria air pollutant and HAPs monitoring data. Detailed air monitoring data for tetrachloroethylene in various locations in the United States for 2006 are shown in Table 6-3 (EPA 2013h). In general, the average concentration of tetrachloroethylene in outdoor air is <1 μg/m^3 (0.15 ppb) for the majority of the U.S. locations sampled; however, five 24-hour average values were measured in Minnesota, New York, Virginia, and Michigan that exceeded 1 μg/m^3.

Tetrachloroethylene was detected in indoor and outdoor air at 0.15–3.5 and 0.01–1.3 μg/m^3, respectively, above a contaminated site in Colorado (Agency for Toxic Substances and Disease Registry 2006).

Measurement of 8-hour time-weighted average exposures in the breathing zones of workers from 196 dry cleaning plants in Australia yielded mean and geometric mean exposure estimates of 10.3 and 4.7 ppm, respectively (NICNAS 2001). About 90% of the exposures were less than 25 ppm, and only 3% of exposures were greater than 50 ppm.

Table 6-3. Tetrachloroethylene Concentrations in Ambient Air for 2006

Concentration (µg/m^3)	Number of samples	State[a]
0.05–0.64	21–70	CA
0.34	61	CO
0.35	61	DC
0.09–0.44	58–59	DE
0.10–0.69	42–61	FL
0.10–0.45	19–61	GA
0.34	59	HI
0.24–0.48	21–26	IA
0.34–0.76	60–61	IL
0.17–0.19	41–61	IN
0.77–0.88	33–61	KY
0.19–0.22	51–52	MA
0.24–0.36	56–61	MD
0.26–1.10	21–50	MI
0.09–6.65	41–58	MN
0.17	59	MO
0.14–0.18	59–66	MS
0.24–0.58	43–58	NC
0.17–0.23	26–31	NH
0.12–0.35	53–58	NJ
0.17–3.32	40–56	NY
0.20	41	OK
0.34	24–61	OR
0.17–0.39	37–61	PA
0.09–0.25	40–57	PR
0.15–0.32	53–61	RI
0.17	60	SC
0.07–0.08	59–61	SD
0.06–0.08	44–45	TN
0.17–0.37	42–61	TX
0.17	59	UT
0.20–1.67	57–60	VA
0.34–0.37	23–54	VT
0.34	61	WI
0.13–0.39	43–51	WV

[a]Post office abbreviations used.

Source: EPA 2013h

In addition, in data reported by the Dow Company in the United States, the TWA exposures were 37, 9, and 5 ppm for first-, third-, and fourth-/fifth-generation dry cleaning machines, respectively. It was discovered that the emissions of tetrachloroethylene were less with the introduction of third- and fourth-/fifth-generation machines, which included an integrated carbon absorber and an interlocking system (to reduce venting) (NICNAS 2001).

In a study conducted by Roda et al. (2013), tetrachloroethylene was found in the indoor air of Paris homes. Air samples were collected using passive devices. Annual levels ranged from 0.6 to 124.2 $\mu g/m^3$ (0.09–18.3 ppb) in residential homes that were in close proximity to dry cleaning facilities and do-it-yourself activities (e.g., photographic development, silverware), had air vents, and were built prior to 1945.

In another locality in France, the highest measured concentration of tetrachloroethylene (678 $\mu g/m^3$) was found in front of a dry cleaning shop in the indoor air of a shopping center. The highest mean concentrations in apartments and establishments directly above the dry cleaning facility ranged from 296 $\mu g/m^3$ (carbon absorber equipped machine) to 2.9 mg/m^3 (carbon absorber unequipped machine). The study was carried out with passive samplers (Chiappini et al. 2009).

In a study conducted in Hudson County, New Jersey, residents above cleaners that used exhaust fans were exposed to concentrations of 1.2 mg/m^3 of tetrachloroethylene, while residents above cleaners that did not use exhaust fans were exposed to 2.5 mg/m^3. Adherence to all of EPA regulations was also associated with decreased tetrachloroethylene levels above dry cleaning facilities. It was found that the mean 48-hour average concentration in residences above cleaners that adhered to EPA's regulations was 0.57 mg/m^3, while the concentration was 2.1 mg/m^3 with cleaners that partially followed EPA's regulations and 2.7 mg/m^3 with cleaners with no documentation of adherence to the rules (Garetano and Gochfield 2000). In an older study, elevated levels of tetrachloroethylene were also found in apartments above dry cleaning facilities (Schreiber et al. 1993). Tetrachloroethylene concentrations ranged from 0.04 to 8.1 ppm in six apartments above dry cleaning facilities when measurements were completed from 7 a.m. to 7 p.m., and from 0.01 to 5.4 ppm when measured from 7 p.m. to 7 a.m. Tetrachloroethylene concentrations were higher above facilities using transfer-type dry cleaning machines compared to dry-to-dry machines, although the highest levels were found above a facility using an old, poorly maintained dry-to-dry machine. Tetrachloroethylene concentrations in nearby apartments were <0.001–0.015 ppm during the day and <0.001–0.01 ppm at night. An EPA final rule has called for the phase out of tetrachloroethylene use in dry cleaners above residential areas (EPA 2006).

Levin and Hodgson (2003) compiled information from 13 studies for exising residences, new residences, and office buildings and compared the central tendency concentrations among each residence or building. The central tendency concentrations were >3 times higher for the office building than for the existing residences. However, even with the prevalence of tetrachloroethylene in office builidngs, the authors concluded that the average indoor concentrations of tetrachloroethylene have decreased since 1990.

Johnston and Gibson (2013) detected tetrachloroethylene in the indoor air of homes of individuals exposed to tetrachloroethylene through soil vapor intrusion. Maximum levels ranged from <0.13 to 1.50 $\mu g/m^3$ in the homes in San Antonio, Texas. Forand et al. (2012) reported that tetrachloroethylene levels ranged from 0.1 to 24 $\mu g/m^3$ in indoor air after residents in the Village of Endicott, New York were exposed to tetrachloroethlyene through vapor soil intrusion. These levels are much higher than the average U.S. indoor residential air concentrations measured by the EPA. Burk and Zarus (2013) reported selected results from 135 vapor intrusion public health assessments and consultations for 121 sites published on ATSDR's website between 1994 and 2009. Tetrachloroethylene indoor air levels were attributed to vapor intrusion and detected at 39 sites; levels at 5 of these sites were high enough to be considered a public health hazard. In addition to vapor instrusion, tetrachloroethylene can also be present in the indoor air of homes from sewer gas emissions coming up through the bathroom plumbing (Pennell et al. 2013).

Tetrachloroethylene was present in 62.5% of background samples collected in North American residences between 1990 and 2005 (EPA 2011). In a study conducted by Sack et al. (1992), 63 out of 1,159 of household products contained tetrachloroethlylene. The percentages of tetrachloroethylene in the household products were 10.8% in automative products, 2.7% in household cleaners/polishes, 1.3% in paint-related products, 18.7% in fabric and leatlher treatments, 2.9% in cleaners for electronic equipment, 8.1% in oils, greases and lubricants, 5.3% in adhesive-related products, and 5.6% in miscellaneous products.

Building occupants can also be exposed to tetrachloroethylene in the indoor air through cleaning products and air fresheners. Ventilation, mixing within a room, mixing between rooms, homogenous and heterogenous transformations, sorptive interactions on surfaces, and active air cleaning are factors that influence the distribution and behavior of tetrachloroethylene in indoor air (Nazaroff and Weschler 2004). Carpet also can also be a source of tetrachloroethylene in indoor air as it sorbs the compound in the fibers of the carpet (Won et al. 2000).

6.4.2 Water

Tetrachloroethylene was detected in 130 of 1,179 well samples in the drinking water from domestic wells in the United States (Rowe et al. 2007).

Williams et al. (2002) reported annual levels of tetrachloroethylene measured in 3,422–4,218 California drinking water sources between 1995 and 2001. Approximately 10–13% of the sampled drinking water sources contained detectable levels over this 7-year period. The average annual detected concentration of tetrachloroethylene ranged from 17.0 µg/L (2000) to 28.0 µg/L (1998).

Tetrachloroethylene and several other volatile organic compounds have been detected at high levels in drinking water at the Camp Lejeune, Marine Corps Base in North Carolina (Agency for Toxic Substances and Disease Registry 1998, 2013). Tetrachloroethylene levels in tap water were shown to range from <1 to 215 µg/L (ppb), and groundwater levels as high as 170,000 µg/L (ppb) were observed in 1985. The maximum contaminant level (MCL) for tetrachloroethylene is 5 µg/L (ppb).

Tetrachloroethylene was monitored in a comprehensive survey conducted by the United States Geological Survey (USGS) of volatile organic compounds in private and public groundwater wells used for drinking water (USGS 2006). Tetrachloroethylene was identified in approximately 4% of 3,498 aquifer samples at a median concentration of 0.090 µg/L for the samples having positive detections. The percentage of samples exceeding the 5 µg/L MCL was 0.70% (USGS 2006). In an analysis of domestic groundwater wells, the median concentration of tetrachloroethylene was reported as 0.058 µg/L for samples having positive detections.

Tetrachloroethylene was detected in groundwater from 16 out of 30 wells located in Salt Lake Valley, Utah, at a maximum concentration of 7.8 µg/L (USGS 2003). Although the median concentration was <0.1 µg/L, water from four wells in the northwestern part of the valley had concentrations >1 µg/L.

In other countries, drinking water samples from Zagreb, Croatia, contained 0.36–7.80 µg/L (0.36–7.80 ppb) (Skender et al. 1993). Rainwater samples collected in Tokyo between October 1989 and September 1990 had a mean tetrachloroethylene level of 99 ng/L (99 ppt), with higher levels in samples obtained during the winter (Jung et al. 1992). The World Health Organization (WHO) guideline value in drinking water for tetrachloroethylene is 40 µg/L (WHO 2010).

The mean detected concentration of tetrachloroethylene in the drinking water of California has been 3–6 times higher than the MCL of 5 µg/L from 1995 to 2000 (Williams et al. 2002). Contamination of drinking water supplies with tetrachloroethylene varies with location and with the drinking water source (surface water or groundwater). Generally, higher levels are expected in groundwater because tetrachloroethylene volatilizes rapidly from surface water. The total daily intake value of ingestion of tetrachloroethylene in drinking water was calculated to be 1.36–2.29 L/day (CEPA 1999).

6.4.3 Sediment and Soil

Soil gas was assessed for contaminants at three former fuel-dispensing sites at Fort Gordon, Georgia, from October 2010 to September 2011. More than half of the 30 soil-gas samplers installed at one location had tetrachloroethylene mass greater than the minimum detection limit (MDL) of 0.02 µg.

The bottom sediments and interstitial water from Watson creek at Aberdeen Proving Ground, Maryland, were found to contain concentrations of tetrachloroethylene ranging from 310 to 550 µg/L. The concentrations in the bottom sediment were found to be similar to observed concentrations of tetrachloroethylene in wells near the shoreline. In addition, tetrachloroethylene in the sediment was found to be an indicator of groundwater contamination (Vroblesky et al. 1991).

6.4.4 Other Environmental Media

Tetrachloroethylene can be absorbed from the atmosphere by foods and concentrated over time, so that acceptable ambient air levels may still result in food levels that exceed acceptable limits (Grob et al. 1990). The study authors estimated that, in order to limit food concentrations of tetrachloroethylene to 50 µg/kg (the maximum tolerated limit for food halocarbons in Switzerland), the level in surrounding air should not exceed 12.5 µg/m^3 (0.002 ppm). Since the accepted levels found near emission sources are often far above this limit, foods processed or sold near these sources may routinely exceed the Swiss tolerated tetrachloroethylene concentration, thus making the setting of air emission standards problematic. It is also noteworthy that the limits recommended by Grob et al. (1990) exceed acceptable ambient air concentrations for many regions of the United States (see Chapter 8).

An analysis of six municipal solid waste samples from Hamburg, Germany, revealed levels of tetrachloroethylene ranging from undetectable to 1.41 mg/kg (1.41 ppm) (Deipser and Stegmann 1994).

In a study analyzing automobile exhaust for chlorinated compounds, tetrachloroethylene was not detected (Hasanen et al. 1979)

In older studies, tetrachloroethylene was detected in a variety of foods ranging from 1 to 230 ng/g (1–230 ppb), with a mean of 12 ng/g (12 ppb) (Daft 1989). An analysis of intermediate grain-based foods in 1985 showed the following tetrachloroethylene levels (in ppb): corn muffin mix, 1.8; yellow corn meal, 0.0; fudge brownie mix, 2.45; dried lima beans, 0.0; lasagna noodles, 0.0; uncooked rice, 0.0; and yellow cake mix, 2.5 (Heikes and Hopper 1986). Levels of tetrachloroethylene detected in margarine from several supermarkets in the Washington, DC, area were 50 ppm in 10.7% of the products sampled (Entz and Diachenko 1988). The highest levels (500–5,000 ppb) were found in samples taken from a grocery store located near a dry cleaning shop. Additional analysis showed that the concentrations were highest on the ends of the margarine stick and decreased toward the middle. According to the study authors, these findings suggested that contamination occurred after manufacturing rather than during the manufacturing process (Entz and Diachenko 1988).

In more recent studies, tetrachloroethylene has been detected in lettuce sap, mid-vein, and mesophyll samples grown on contaminated soils (Boekhold et al. 1989). Tetrachloroethylene has also been detected in fatty foods such as butter, cream, vegetable oil, margarine, sausage, and cheese in residences or food stores near dry cleaners (Schreiber et al. 1993).

In Switerzland, the highest concencentration of tetrachloroethylene was in the milk and meat products at 3–3490 µg/kg. In Germany, in a dry cleaning shop and in an apartment above a dry cleaning shop, concentrations of tetrachloroethylene were highest in an ice-cream confection at 18,750 µg/kg and butter at 58,000 µg/kg. The total daily intakes for Switerzland and Germany were 160 and 87 µg/day, respectively (de Raat 2003).

Likewise, tetrachloroethylene can be present in breast milk. Pellizzaari et al. (1982) found that tetrachloroethylene was present as frequent as seven times in the eight samples analyzed from the mother’s milk in four urban areas. Bagnell and Ellenberger (1977) also observed tetrachloroethylene in a mother’s milk in a case study that resulted in the baby getting sick with obstructive jaundice and hepatomegaly.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The most important routes of exposure to tetrachloroethylene for most members of the general population are inhalation of the compound in the indoor and outdoor (ambient) air and ingestion of contaminated drinking water. Available data generally indicate that dermal exposure is not an important route for most people. General population exposure from inhalation of the indoor and outdoor (ambient) air varies widely depending on location. While background levels are generally in the low-ppt range in rural and remote areas, values in the high-ppt and low-ppb range are found in urban and industrial areas and areas near point sources of pollution.

Tetrachloroethylene exposure was measured in the population of children from two inner-city schools in Minneapolis, Minnesota. Concentrations ranged from 0.1 to 1.3 $\mu g/m^3$ in four locations, including outdoors, outdoors at school, indoors at home, and personal VOC samples. It was found that the indoor air at home contained the highest levels of tetrachloroethylene, followed by the personal samples, outdoors, and indoors at school (Adgate et al. 2004).

Tetrachloroethylene in the ambient air was assessed in Tokyo with participants who were not directly exposed to tetrachloroethylene in their workplace. It was found that the mean levels of tetrachloroethylene in the breathing air was 1.1 ± 0.8 $\mu g/m^3$ and the daily intake was calculated to be 23 µg/person (Nakahama et al. 1997).

Indoor air of apartments where dry cleaners lived was about 0.04 ppm compared to 0.003 ppm in the apartments of the controls (Aggazzotti et al. 1994a), indicating that dry cleaners serve as a source of exposure for their families. Breath concentrations of tetrachloroethylene in dry cleaners, family members, and controls were 0.65, 0.05, and 0.001 ppm, respectively (Aggazzotti et al. 1994b). A study that combined PBPK modeling with a single compartment model for a "typical" home (Thompson and Evans 1993) suggested that tetrachloroethylene levels in a home with a worker exposed to a TWA of 50 ppm for 8 hours as the only source of tetrachloroethylene could result in concentrations of 0.004–0.01 ppm. The air exchange rate in the house made a larger difference in the house air concentrations than the choice of metabolic data used in the PBPK model.

The Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2012*)* provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals by the use of biomonitoring (CDC 2012). Blood concentrations of tetrachloroethylene ranged from below the limit of

detection up to 0.14 ng/mL in a random sampling of 1,317 participants in the 2003–2004 U.S. NHANES survey. Table 6-4 provides the geometric means.

Higher blood levels of tetrachloroethylene have been noted for urban and industrial residential settings when compared to rural settings. Residing near dry cleaning facilities or storing recently dry-cleaned clothes at home can contribute to increased blood tetrachloroethylene levels. In occupationally exposed workers, tetrachloroethylene blood levels have been reported to be many thousand times higher than in the unexposed general population.

Tetrachloroethylene has been measured in the blood and urine in a sample of the general population in Italy (Brugnone et al. 1994). In rural locations, tetrachloroethylene was detected in the blood of 76% of 107 individuals tested at a mean concentration of 62 ng/L, while in 106 urban subjects, it was detected in 41% at a mean concentration of 263 ng/L. Measurement of tetrachloroethylene in urine showed similar results for rural (74% positive; average 119 ng/L) and urban populations (74% positive; average 90 ng/L). Tetrachloroethylene was also detected in urine samples of dry cleaning workers at concentrations of 1–19.9 µg/L (Rutkiewicz et al. 2011). In Zagreb, Croatia, tetrachloroethylene concentrations ranged from 210 to 7,800 ng/L in the drinking water and from <10 to 239 ng/L in blood (Skender et al. 1994).

Although the use of tetrachloroethylene in the dry cleaning industry makes this chemical a potential hazard for exposed workers, casual contact by the general population with dry-cleaned clothing may pose a slight risk as well. One study showed that the storage of newly dry-cleaned garments in a residential closet resulted in tetrachloroethylene levels of 0.5–2.9 mg/m^3 (74–428 ppb) in the closet after 1 day, followed by a rapid decline to 0.5 mg/m^3 (74 ppb), which persisted for several days (Tichenor et al. 1990). Initial "airing out" of the clothes for 4–8 hours had little effect on the resulting emissions, presumably because diffusion through the fabric, rather than surface evaporation, was rate-limiting. A study of nine homes into which ≤10 freshly dry-cleaned garments were introduced showed an increase in tetrachloroethylene levels in the air of seven homes (Thomas et al. 1991). The increases ranged from 2 to 30 times the levels before the introduction of the garments, and the magnitude of the increase was highly correlated with the number of garments divided by the house volume. Tetrachloroethylene levels in personal breathing space and expired air of residents were also monitored and found to be generally correlated with indoor air concentrations. An investigation of different methods for reducing tetrachloroethylene retention in dry-cleaned fabrics found that, while airing at 20°C for several hours had little effect, airing at 45°C greatly reduced retention time, and was thus recommended as a way to reduce consumer exposure from garments (Guo et al. 1990).

Table 6-4. Geometric Mean and Selected Percentiles of Tetrachloroethylene Blood Concentrations (in ng/mL) for the U.S. Population from NHANES

	Survey	Geometric mean	50th percentile	75th percentile	90th percentile	95th percentile	Sample size
Total	2001–2002	*[a]	<LOD	0.50	0.100	0.190	978
	2003–2004	*	<LOD	<LOD	0.076	0.140	1317
20–59 years age	2001–2002	*	<LOD	0.50	0.100	0.190	978
20–59 years age	2003–2004	*	<LOD	<LOD	0.076	0.140	1317
Males	2001–2002	*	<LOD	0.50	0.110	0.210	457
Males	2003–2004	*	<LOD	<LOD	0.082	0.230	639
Females	2001–2002	*	<LOD	0.50	0.100	0.150	521
Females	2003–2004	*	<LOD	<LOD	0.069	0.120	678
Mexican/American	2001–2002	*	<LOD	<LOD	0.060	0.070	226
Mexican/American	2003–2004	*	<LOD	<LOD	0.049	0.110	248
Non-Hispanic blacks	2001–2002	*	<LOD	<LOD	0.070	0.110	195
Non-Hispanic blacks	2003–2004	*	<LOD	<LOD	0.086	0.220	284
Non-Hispanic whites	2001–2002	*	<LOD	0.50	0.110	0.210	487
Non-Hispanic whites	2003–2004	*	<LOD	<LOD	0.072	0.140	686

[a]The geometric mean was not calculated because the proportion of the results below LOD was too high to provide a valid result.

LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2012

A survey of 15 coin-operated dry cleaning establishments in Hamburg, Germany, showed indoor air concentrations of tetrachloroethylene between 3.1 and 331 mg/m^3 (457 and 48,812 ppb) and a concentration of 4.5 mg/m^3 (664 ppb) in one building 7.5 months after removal of dry cleaning machines, indicating that tetrachloroethylene may be absorbed by building materials and then slowly released into the air over time (Gulyas and Hemmerling 1990). This study also indicated that a car transporting a freshly dry-cleaned down jacket had air concentrations of 20.4 mg/m^3 (3,008 ppb) after 25 minutes and 24.8 mg/m^3 (3,657 ppb) after 108 minutes.

A survey of dry cleaning operators conducted by the International Fabricare Institute from 1980 to 1990 indicated that 1,302 operators in plants with transfer units were exposed to a TWA of 48.4 ppm, while 1,027 operators in plants with dry-to-dry units were exposed to a TWA of 16.9 ppm (Andrasik and Cloutet 1990). An in-depth series of studies of the dry cleaning industry was completed by NIOSH in 1997. These studies evaluate worker exposure to tetrachloroethylene at several locations in the United States and examine how the exposure can be controlled (Earnest 1995, 1996; Earnest and Spencer 1995; Earnest et al. 1995a, 1995b, 1995c; Spencer et al. 1995). Personal and area air samples were obtained. Results of the studies showed that the TWA concentrations of tetrachloroethylene were within the ACGIH recommended threshold limit value of 25 ppm (ACGIH 2012). The primary exposure of the workers occurred during the loading and unloading of the dry cleaning machines.

A study was conducted on the exposure of workers in six commercial and three industrial dry cleaners. It was found that the operator's mean TWA exposures in the commercial dry cleaning shops and industrial cleaners were 4.1 and 4.6 ppm. Both the presser and the customer service personnel had significantly lower TWA exposures of 0.5 and 0.1 ppm, respectively. The results were again lower than the occupational limit values in the United States, with the outdoor tetrachloroethylene emissions below the limit values (Raisanen et al. 2001).

In a study conducted in Iran, concentrations of tetrachloroethylene uptake went from 6.58 µg/L before exposure to 18.04 µg/L after the end of the shift (post exposure) with an 8 kg dry cleaning machine. Likewise, concentrations increased from 14.17 to 36.77 µg/L with a 12-kg dry cleaning machine and from 21.95 to 63.55 µg/L in an 18-kg dry cleaning machine (Rastkarie et al. 2011).

Individuals are not exposed to the same magnitude of tetrachloroethylene as in the past. In a study conducted in Italy, the mean concentration of tetrachloroethylene in the air was 52.32 mg/m^3 with

tetrachloroethylene concentrations in the blood end-shift at 0.617 mg/L (pre-shift: 0.304 mg/L) and in the urine at 0.0204 mg/L (pre-shift: 0.012). It was also found that the smaller shops that employed 1–3 people had the greatest exposure to tetrachloroethylene (Macca et al. 2012).

In addition, a biological exposure assessment was done with female workers in an Ohio dry cleaning facility. Four dry cleaning facilities and 18 women participated in the assessment. The dry cleaning machines were 30–60-pound drums and ranged from 9 to 12 years old. Personal breathing zone samples, as well as blood, urine, and post-shift exhaled breath samples, were collected for the women. It was found that post-shift exhaled breath tetrachloroethylene increased during the week from 0.94 ppm on Wednesday to 1.38 ppm on Thursday and to 1.63 ppm on Friday; however, the tetrachloroethylene in exhaled breath and urine decreased after 2 days without renewed exposure to tetrachloroethylene (McKernan et al. 2008).

Various consumer products have been found to contain tetrachloroethylene. These include printing ink, glues, sealants, polishes, lubricants, and silicones (ACGIH 1991). In addition, VOCs may be emitted from cleaners, air fresheners, scented candles, carpets, insulation, paint, etc. Tetrachloroethylene was detected in 64% of samples of indoor background air from 1990 in residences not affected by vapor intrusion (Dawson and McAlary 2009).

Showering or bathing with contaminated water can also result in tetrachloroethylene exposure. Rao and Brown (1993) described a combined PBPK exposure model that estimates brain and blood levels of tetrachloroethylene following a 15-minute shower or 30-minute bath with water containing 1 mg tetrachloroethylene/L. The PBPK model is described further in Section 3.4.5. The exposure model assumed that the shower or bath would use 100 L of water, the air volume in the shower stall or above the bath tub was 3 m^3, and the shower flow rate was 6.667 L/minute. The exposure model was validated with data for chloroform and trichloroethylene, but not tetrachloroethylene. Using this model, Rao and Brown (1993) estimated that shower air would contain an average of 1 ppm and that the air above the bathtub would contain an average of 0.725 ppm if the water contained 1 mg tetrachloroethylene/L.

Total tetrachloroethylene intake for Canadians has been estimated to range from 1.2 to 2.7 µg/kg/day (CEPA 1993). Indoor air exposure (assuming 20 hours/day) from the use of household products containing tetrachloroethylene and from recently dry-cleaned clothes accounted for 1.2–1.9 µg/kg/day. Drinking water and food consumption contributed 0.002–0.03 and 0.12–0.65 µg/kg/day, respectively. Data were not sufficient to estimate tetrachloroethylene intake from soil.

The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated that 688,110 workers employed at 49,025 plant sites were potentially exposed to tetrachloroethylene in the United States during this period (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

In addition to breathing air or consuming contaminated water, infants can also be exposed to tetrachloroethylene in breast milk. Tetrachloroethylene was present at unspecified levels in seven of eight samples of mother's milk from four urban areas in the United States (Pellizzari et al. 1982). A woman in Halifax, Nova Scotia, who visited her husband daily at the dry cleaning plant where he worked, was found to have tetrachloroethylene present in her breast milk (Bagnell and Ellenberger 1977). This was discovered after her breast-fed infant developed obstructive jaundice, which was attributed to the contaminant. Using a PBPK model, Schreiber (1993) predicted that for women exposed under occupational conditions, breast milk concentrations would range from 857 to 8,440 μg/L. The exposure scenarios for the low concentrations were 8 hours at about 6 ppm (exposure concentration of counter workers, pressers, and seamstresses) and 16 hours at 0.004 ppm (residential background), and for the high concentration, exposure scenarios were 8 hours at 50 ppm and 16 hours at 0.004 ppm (residential background). Assuming that a 7.2-kg infant ingests 700 mL of breast milk/day, the infant dose would range from 0.08 to 0.82 mg/kg/day. The infant dose estimated from background exposure (24 hours at

0.004 ppm) was 0.001 mg/kg/day (Schreiber 1993). Because of potential widespread exposure, the study author suggested that additional monitoring of breast milk levels should be completed. A second model of the lactational transfer of tetrachloroethylene has been developed using data from rats (Byczkowski and Fisher 1994, 1995). Using an exposure scenario similar to that described by Bagnell and Ellenberger (1977), investigators (Byczkowski and Fisher 1994) estimated that a 1-hour exposure to 600 ppm tetrachloroethylene each day would result in an infant blood concentration of about 0.035 mg/L within 1 month of exposure. Using the same exposure scenarios as Schreiber (1993), the Byczkowski and Fisher (1995) model predicts slightly smaller doses delivered to the infant. For example, Schreiber (1993) predicted 0.08 mg/kg/day as the minimum dose to the infant for the exposure scenario for low concentrations (8 hours at 6 ppm, 16 hours at 0.004 ppm), while Byczkowski and Fisher (1995) predicted a dose of 0.032 mg/kg/day. The Schreiber (1993) model may have overestimated the dose to the infant because it assumes that the infant will be exposed to the peak concentrations of tetrachloroethylene in breast milk, while the Byczkowski and Fisher (1995) model provides more insight into the changing concentrations of tetrachloroethylene in breast milk as maternal exposure changes.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Various segments of the population can be exposed to levels of tetrachloroethylene significantly above normal background concentrations. Metal degreasers who use the chemical as a solvent would be expected to have high exposure. People working in the dry cleaning industries are exposed to elevated levels of tetrachloroethylene. In addition, evidence suggests that people living with workers in the dry cleaning industry may be subjected to higher exposures, even if their homes are far removed from the work site (Aggazzotti et al. 1994a); 30 such homes surveyed showed a range of indoor tetrachloroethylene levels of 34–3,000 μg/m^3 (5.0–442 ppb), which was significantly higher than that found in control homes (1–16 μg/m^3 or 0.1–2.4 ppb). The tetrachloroethylene levels in alveolar air samples were likewise significantly higher in family members of workers than in control subjects, and the higher exposures were attributed to clothing worn home from work and the expired breath of workers (Aggazzotti et al. 1994a, 1994b).

Service members and their families stationed at the Camp Lejeune Marine Corps Base, North Carolina were exposed to high levels of tetrachloroethylene and other VOCs from bathing in and consuming contaminated water (Agency for Toxic Substances and Disease Registry 2013).

Residents living in apartment buildings in New York City also housing dry cleaners were exposed to higher levels of tetrachloroethylene (indoor air level of 27.5 μg/m^3), as compared to residents living in buildings without a dry cleaner (2.3 μg/m^3) (Storm et al. 2013). When the residents were categorized by minority status, the mean level of tetrachloroethylene in the indoor air was 82.5 μg/m^3 in the minorities living in apartments buildings with dry cleaners, compared to 16.5 μg/m^3 in non-minority households living in the buildings with dry cleaners. No differences in indoor air levels were found between minority and non-minority residents living in buildings without dry cleaners. Mean indoor tetrachloroethylene air levels were also higher in low income family homes in buildings with dry cleaners (105.5 μg/m^3) compared to high income family homes in buildings with dry cleaners (17.8 μg/m^3). Likewise, mean blood tetrachloroethylene levels in residents living in apartment buildings with dry cleaners were 0.27 ng/mL in minority children and 0.46 ng/mL in minority adults, while mean blood levels were 0.12 ng/mL in non-minority children and 0.15 ng/mL in non-minority adults. The same trend was observed in low income children and adults, where mean blood levels were 3 and 4 times higher than the levels of the high income children and adults. The study shows that residents living in buildings with co-located dry cleaners in minority, low-income areas have higher exposures to tetrachloroethylene than residents living in buildings with co-located dry cleaners in non-minority high income areas (Storm et al. 2013).

Similarly, 37.1–62.6% of blood samples were above the detection limits for tetrachloroethylene in a School Health Imitative: Environment, Learning, Disease (SHIELD) study of children attending schools in minority neighborhoods in Minneapolis, Minnesota (Sexton et al. 2005). Exposure was due to multiple media including air, water, soil, dust, food, beverages, and consumer products. Blood levels ranged from 0.02 to 0.82 ng/mL and were generally ≥2 times lower when compared to concentrations in nonsmoking and smoking adults from the NHANES III study.

Elevated levels of tetrachloroethylene in human breath of the general public (i.e., non-occupational exposure) appear to be related to tetrachloroethylene emissions from nearby factories or from chemical waste dumps. A sample of six children living near a factory in the Netherlands had a mean concentration of 24 μg/m^3 (3.5 ppb) tetrachloroethylene in their breath, compared with 11 control children with a mean level of 2.8 μg/m^3 (0.4 ppb) (Monster and Smolders 1984). Nine residents of Love Canal, New York, a site of serious chemical contamination for many years, were found to have tetrachloroethylene levels ranging from 600 to 4,500 ng/m^3 (0.09–0.66 ppb) in their breath, from 0.35 to 260 ng/mL (0.35–260 ppb) in their blood, and from 120 to 690 ng/mL (120–690 ppb) in their urine (Barkley et al. 1980). This same

study indicated that the participants were exposed to 120–14,000 ng/m^3 (0.02–2.06 ppb) in ambient outside air and levels of 350–2,900 ng/L (0.35–2.90 ppb) in their drinking water.

Because of its pervasiveness in the environment, the general public can be exposed to tetrachloroethylene through drinking water, air, or food, although the levels of exposure are probably far below those causing any adverse effects. Concern may be justified, however, for people who are continuously exposed to elevated levels, such as residents of some urban or industrialized areas, people living near hazardous waste sites, or people exposed at work. Short-term exposure to high levels of tetrachloroethylene may also pose risks to people using products containing the chemical in areas with inadequate ventilation. The discontinuation of tetrachloroethylene use in many medical applications and some consumer products has generally decreased the exposure risks in these situations.

An EPA TEAM (Total Exposure Assessment Methodology) study conducted in New Jersey attempted to identify factors associated with risk of higher inhalation of tetrachloroethylene (Wallace et al. 1986b). The following factors (in order of importance) were identified: employment (not otherwise specified), wood processing, visiting a dry cleaner, working at a textile plant, using pesticides, and working at or being in a paint store.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tetrachloroethylene is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tetrachloroethylene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of tetrachloroethylene are well characterized and allow prediction of the environmental fate of the compound (HSDB 2013; Lide 2008). Estimates of the distribution of tetrachloroethylene in the environment based on available constants (e.g., water solubility, log K_{ow}, log K_{oc}, vapor pressure) (HSDB 2013; Seip et al. 1986) are generally in good agreement with experimentally determined values. Carpet is a source of tetrachloroethylene in the indoor air (Won et al. 2000). Additional information on tetrachloroethylene partitioning between indoor air and building materials is needed, as well as information on the sorption kinetics for those materials.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2011, became available in November of 2012. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Humans are at risk of exposure to tetrachloroethylene because of its widespread use and distribution in the environment. Production, import, and use of the chemical are known to be relatively high. Tetrachloroethylene is released to the atmosphere mainly through its use in the dry cleaning and textile processing industries, as a chemical intermediate, and in degreasing procedures (Dow 2008; HSDB 2013). It is also released to surface water and land in sewage sludges and industrial liquid or solid waste (Schultz and Kjeldsen 1986; Weant and McCormick 1984). Tetrachloroethylene-containing material is considered a hazardous waste and its disposal is subject to regulations (EPA 2007). More current data on production, use in food processing and consumer products, releases, efficiency of disposal practices, adequacy of current disposal regulations, and the extent of recovery and recycling of tetrachloroethylene would assist in estimating human potential exposures, particularly of populations living near industrial facilities and hazardous waste sites.

Environmental Fate. Tetrachloroethylene partitions primarily to the atmosphere (Class and Ballschmiter 1986), where it can be transported back to land and surface water in rain (Pearson and McConnell 1975; Su and Goldberg 1976). In air, the half-life of tetrachloroethylene has been estimated to range from 70 to 251 days (Class and Ballschmiter 1986; Cupitt 1987). Tetrachloroethylene can be biodegraded under the appropriate conditions in soil (Cabirol et al. 1996, 1998; Chang et al. 1998, 2011;

Isalou et al. 1998; Kim et al. 2010; Krumholz et al. 1996) and groundwater (Cichocka et al. 2010; Hunkeler et al. 1999; Sharma and McCarty 1996,). However, the non-aqueous phase is quite difficult to treat and as a result, tetrachloroethylene persists at many hazardous waste sites (Chilton et al. 1990; Doust and Huang 1992). Vapor-phase tetrachloroethylene can migrate up from contaminated water or soil to above ground inside a home or building through vapor intrusion (Agency for Toxic Substances and Disease Registry 2006; Forand et al. 2012; Johnston and Gibson 2013; NYYSDH 2006). More studies are needed to investigate the environmental fate of subsurface tetrachloroethylene, especially with regard to vapor intrusion. The hydrolysis half-life has been estimated to be from 9 months (Dilling et al. 1975) to $9.9x10^8$ years (Jeffers et al. 1989). Because of the great variability in half-life, additional studies regarding the hydrolysis of tetrachloroethylene would be useful.

Bioavailability from Environmental Media. No studies have been identified regarding the absorption of tetrachloroethylene following ingestion of contaminated soil and plants grown on contaminated soil near hazardous waste sites and other point sources of pollution. Tetrachloroethylene can be absorbed following inhalation (Hake and Stewart 1977; Monster et al. 1979), oral (Frantz and Watanabe 1983; Pegg et al. 1979; Schumann et al. 1980), or dermal exposure (Jakobson et al. 1982; Stewart and Dodd 1964; Tsuruta 1975). All of these routes of exposure may be of concern to humans because of the potential for tetrachloroethylene to contaminate the air, drinking water, food, and soil. More information on the absorption of tetrachloroethylene following ingestion of contaminated soil and plants grown on contaminated soil near hazardous waste sites and other sources of pollution would be helpful in determining the bioavailability of the chemical from soil.

Food Chain Bioaccumulation. Data indicate that tetrachloroethylene has a low bioconcentration potential in aquatic organisms, animals and plants (Barrows et al. 1990; Kawasaki 1980; Kenaga 1980; Neely et al. 1974; Polder et al. 1998; Saisho et al. 1994; Veith et al. 1980). Although biomagnification of tetrachloroethylene in terrestrial and aquatic food chains is not expected to be important because the compound is metabolized in animals, experimental data to confirm the expected behavior would be useful in evaluating the importance of food chain bioaccumulation as a source of human exposure to tetrachloroethylene.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of tetrachloroethylene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of tetrachloroethylene in the environment can be used in combination with the known

body burden of tetrachloroethylene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Tetrachloroethylene is widely distributed in the environment and has been detected in air (Adgate et al. 2004; Aggozzotti et al. 1994a; Roda et al. 2013), water (Dykson and Hess 1982; Lee et al. 2002; Rao and Brown et al. 1993; Ligocki et al. 1985; Rowe et al. 2007; Williams et al. 2002), soil (Vroblesky et al. 1991), and food (Daft 1989; Entz and Diachenko 1988; Entz and Hollifield 1982; Grob et al. 1990; Heikes and Hopper 1986). Tetrachloroethylene was found to be present in lettuce, and is prevalent in other fruits and vegetables (Boekhold et al. 1989; de Raat 2003). Additional data on the occurrence of tetrachloroethylene in foods would be important in understanding how the compound contaminates the food.

Ambient air levels in cities in the United States generally range from 0.035 to 1.3 ppb (Hartwell et al. 1987). Continual monitoring data for surface air, water, groundwater, and soil are needed to assess the current potential for exposure to the chemical from these media. Additional data characterizing the concentration of tetrachloroethylene in air, water, and soil surrounding hazardous waste sites and estimating human intake from these media would be helpful in assessing the potential human exposure to this chemical for populations living near hazardous waste sites.

Exposure Levels in Humans. Tetrachloroethylene has been detected in human breath (Aggazzotti et al. 1994b; Koppel et al. 1985; Stewart et al. 1977), blood (Altmann et al. 1990; Brugnone et al. 1994; Hattis et al. 1993; Skender et al. 1994), urine (Koppel et al. 1985; Rutkiewicz et al. 2011), tissues (Garnier et al. 1996; Levine et al. 1981; Lukaszewski 1979), and breast milk (Bagnell and Ellenberger 1977). Most of the monitoring data come from occupational studies of specific worker populations exposed to tetrachloroethylene (McKernan et al. 2008; Raisanen et al. 2002); however, some studies of exposure in the general population have been done (CDC 2012; Chiappini et al. 2009; Garetano and Gochfeld 2000; Roda et al. 2013; Zocollio et al. 2009). Because infants may be more susceptible to tetrachloroethylene, more information on tetrachloroethylene in breast milk would be useful. Data correlating levels in biological samples with media exposure levels and the subsequent development of health effects are especially needed for populations living in the vicinity of hazardous waste sites. There are data that suggest that levels of tetrachloroethylene among minorities who live in buildings with a dry cleaner are higher than non-minority levels (Storm et al. 2013); however, there is a need for more studies that focus on minority populations and their exposure to tetrachloroethylene.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Limited data are available regarding the exposures of children to tetrachloroethylene. Tetrachloroethylene was present at unspecified levels in breast milk samples (Bagnell and Ellenberger 1977; Pellizzari et al. 1982). Using a PBPK model, Schreiber (1993) predicted that for women exposed under occupational conditions, breast milk concentrations would range from 857 to 8,440 μg/L. Using an exposure scenario similar to that described by Bagnell and Ellenberger (1977), other investigators (Byczkowski and Fisher 1994) estimated that a 1-hour exposure to 600 ppm tetrachloroethylene each day would result in an infant blood concentration of about 0.035 mg/L within 1 month of exposure. Additional information regarding the levels of tetrachloroethylene in these and other matrices, such as tissue, neonatal blood, cord blood, and meconium fluid, would be helpful in assessing the exposure of children to this substance.

Child health data needed to inform age-related susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for tetrachloroethylene were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

Ongoing studies pertaining to tetrachloroethylene have been identified and are shown in Table 6-5.

Table 6-5. Ongoing Studies on Tetrachloroethylene

Principal Investigator	Study topic	Institution	Sponsor
Vaidya, B	Development of a field deployable vapor intrusion monitor for VOCs such as tetrachloroethylene	Lynntech, Inc., College Station, Texas	National Institute of Environmental Health Sciences
Leen, JB	Development of a laser-based spectrometer for real-time monitoring of VOCs (including tetrachloroethylene) at superfund sites	Los Gatos Research, Mountain View, California	National Institute of Environmental Health Sciences

VOC = volatile organic compound

Source: RePORTER 2013

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring tetrachloroethylene, its metabolites, and other biomarkers of exposure and effect to tetrachloroethylene. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Several methods are available for the analysis of tetrachloroethylene in biological media. The method of choice depends on the nature of the sample matrix; required precision, accuracy, and detection limit; cost of analysis; and turnaround time of the method. Since tetrachloroethylene is metabolized in the human body to trichloroacetic acid, trichloroacetic acid may be quantified in blood and urine as an indirect measure of tetrachloroethylene exposure (Monster et al. 1983). It should be pointed out that the determination of trichloroacetic acid may not provide unambiguous proof of tetrachloroethylene exposure since it is also a metabolite of trichloroethylene. Trichloroethanol has also been thought to be a metabolite of tetrachloroethylene, identified following occupational exposure (Birner et al. 1996; Ikeda et al. 1972; Monster et al. 1983). However, rather than being a metabolite of tetrachloroethylene, it is more likely that trichloroethanol is formed from trichloroethylene, which is often found as a contaminant of tetrachloroethylene (Skender et al. 1991). Methods for the determination of trichloroethylene and trichloroethanol are summarized in the Toxicological Profile for Trichloroethylene (Agency for Toxic Substances and Disease Registry 1997).

The main method used to analyze for the presence of tetrachloroethylene and trichloroacetic acid in biological samples is separation by gas chromatography (GC) combined with detection by mass spectrometry (MS) or an electron capture detector (ECD). Tetrachloroethylene and/or its metabolites have been detected in exhaled air, blood, urine, breast milk, and tissues. Preconcentration techniques are frequently used in tetrachloroethylene analysis. Preconcentration not only increases the sensitivity, but in certain instances, may also decrease the sample separation time. Interference in tetrachloroethylene

analysis results from the widespread distribution of volatile organic compounds in the environment. The most likely sources of these interfering compounds are contamination from the vessels used to hold and prepare samples, contamination of the plumbing in the analytical instrument, and leaking of environmental contaminants into the sample vessel. Details on sample preparation, analytical method, and sensitivity and accuracy of selected methods are shown in Table 7-1.

Breath samples have been analyzed for tetrachloroethylene in several studies. Preconcentration on a solid sorbent followed by thermal desorption onto a cryogenic trap connected to the gas chromatograph was used to analyze exhaled air in several TEAM studies (Wallace 1986; Wallace et al. 1986a, 1986b, 1986c, 1986d). Vapors were thermally released directly onto the chromatographic column for separation and detection by electron impact MS (EIMS).

The methods most frequently used to determine the presence of tetrachloroethylene in biological tissues and fluids are headspace analysis and purge-and-trap, followed by GC/MS or GC/ECD. In headspace analysis, the gaseous layer above the sample is injected into the gas chromatograph. Samples may be hydrolyzed prior to analysis of headspace gases (Ramsey and Flanagan 1982). Headspace gases can be preconcentrated prior to GC analysis (Cramer et al. 1988; Michael et al. 1980) or injected directly into the gas chromatograph (Ramsey and Flanagan 1982). Sensitivity is in the low-ppb range, with generally good precision and accuracy for blood, serum, plasma, and urine (Cramer et al. 1988; Michael et al. 1980). The purge-and-trap method is used with liquid samples and involves purging the sample with an inert gas and trapping the purged volatiles on a solid sorbent. Blood and breast milk have been analyzed for tetrachloroethylene by purging onto a solid sorbent to concentrate the volatiles, followed by thermal desorption and analysis by GC/MS (Antoine et al. 1986; Pellizzari et al. 1982). However, the breast milk analysis was only qualitative, and recoveries appeared to be low for those chemicals analyzed (Pellizzari et al. 1982). Precision and sensitivity were comparable to headspace analysis, but accuracy was lower. Recovery of tetrachloroethylene from rat tissues was found to be greater when the tissues were homogenized in saline:isooctane (1:4) rather than saline alone (Chen et al. 1993).

Analysis of blood and urine for trichloroacetic acid has been done primarily by GC/ECD (Ziglio et al. 1984). Trichloroacetic acid has also been determined colorimetrically by decarboxylation to chloroform and conjugation with pyridine (Pekari and Aitio 1985a). The recovery and precision for this method were good, but the sensitivity was about a tenth that of GC/ECD methods (Christensen et al. 1988; Pekari and Aitio 1985a).

Table 7-1. Analytical Methods for Determining Tetrachloroethylene in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Exhaled air	Collected in spirometer; pre-concentrated on Tenax-GC; thermally desorbed	HRGC/MS	0.3 ppb	95–99	Wallace et al. 1986a, 1986d
Blood	Thermally decarboxylated; subjected to static head-space analysis	GC/ECD (for metabolite TCA)	2 ppb	101–109	Ziglio et al. 1984
Blood	Antifoam agent added; purged and trapped on Tenax-GC/silica gel; thermally desorbed	GC/MS	0.5 ppb	Not reported	Antoine et al. 1986
Blood	Sealed in gas-tight vial; heated, subjected to static head-space analysis	GC/PID, ECD, and FID	68 ng/L (GC/PID), less than the detection limit (ECD), and 35 ng/L (FID)0.005–0.0012 µg/L	Not reported	Schroers et al. 1998
Blood	Stored in vacutainers at 4 °C in the dark, transferred to SPME vial, and subjected to SPME headspace analysis	GC-MS		Not reported	Blount et al. 2006
Blood, plasma, and serum	Sample in sealed vial subjected to static head-space analysis	GC/ECD	100 ppb	Not reported	Ramsey and Flanagan 1982
Blood, urine, and adipose tissue	Passed inert gas over head-space of sample and trapped on Tenax-GC; thermally desorbed	HRGC/MS	Not reported	100 (blood); 72 (urine); 52 (adipose tissue)	Michael et al. 1980
Urine	Thermally decarboxylated; reacted with pyridine	Spectro-photometry (for metabolite TCA)	<0.8 ppm	93.5	Pekari and Aitio 1985a
Urine	Enzyme hydrolysis of sample; decarboxylation of trichloroacetic acid; head-space gas analyzed	GC/ECD (for metabolite TCA)	20 ppb	98	Christensen et al. 1988

Table 7-1. Analytical Methods for Determining Tetrachloroethylene in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Hydrolyzed with H_2SO_4; extracted with isooctane	GC/ECD (for metabolite trichloro-ethylene)	75 ppb	98.2	Pekari and Aitio 1985b
Urine	Stored in vacutainers, subjected to SPME headspace analysis	GC-MS	0.005 µg/L	Not reported	Poli et al. 2005
Tissue	Mixed with a proteolytic enzyme; incubated at 65°C; head-space gas analyzed	GC/ECD	NR	100	Ramsey and Flanagan 1982
Tissue	Homogenization in saline; extraction into isooctane; or direct homogenization into saline:isooctane; head-space gas analyzed	GC	1 ng	Saline homogenization, 69–105; isooctane homogenization, 81–99	Chen et al. 1993
Human milk	Purged warm; trapped in Tenax-GC; thermally desorbed	HRGC/MS	Qualitative identification	Not reported	Pellizzari et al. 1982

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HRGC = high resolution gas chromatography; H_2SO_4 = sulfuric acid; MS = mass spectrometry; PID = photoionization detector; SPME = solid-phase microextraction; TCA = trichloroacetic acid

Static headspace capillary GC with serial triple detection is also a sensitive and reliable method for the determination of tetrachloroethylene in blood. Tetrachloroethylene is able to be separated out easily due to its volatility by headspace techniques. The detection limits for the photoionization detector (PID), ECD, and flame ionization detector (FID) were 68 ng/L, less than the detection limit, and 35 ng/L, respectively (Schroers et al. 1998).

Novel methods of detecting tetrachloroethylene in biological samples have been developed recently. Headspace solid-phase microextraction (SPME) GC-MS was utilized to effectively determine the concentration of tetrachloroethylene in exposed (0.58 µg/L) and non-exposed individuals (0.11 µg/L). Detection limits were 0.005 µg/L (Poli et al. 2005) and 0.005–0.12 µg/L (Blount et al. 2006).

7.2 ENVIRONMENTAL SAMPLES

Analysis of environmental samples is similar to that of biological samples. The most common methods of analyses are GC coupled to MS, ECD, a Hall's electrolytic conductivity detector (HECD), or a FID. Preconcentration of samples is usually done by sorption on a solid sorbent for air and by the purge-and-trap method for liquid and solid matrices. Alternatively, headspace above liquid and solid samples may be analyzed without preconcentration. Details of commonly used analytical methods for several types of environmental samples are presented in Table 7-2.

The primary methods of analyzing for tetrachloroethylene in air are GC combined with either MS or ECD. Air samples are collected on a solid sorbent, thermally desorbed to an on-column cryogenic trap and heat-released from the trapping column directly to the gas chromatograph (Bayer and Black 1987; EPA 1999a; EPA 1999b; Krost et al. 1982; Wallace 1986; Wallace et al. 1986a, 1986b, 1986c, 1986d). Grab-samples of air can also be obtained and preconcentrated on a cryogenic column (Makide et al. 1979; Rasmussen et al. 1977). EPA Method TO-15 (EPA 1999a) and Method TO-17 (EPA 1999b) are identical, except that Method TO-17 uses an alternative sampling technique (direct sampling to solid sorbent tubes) rather than the collection in specially prepared stainless steel canisters followed by concentration using a solid sorbent and then thermal desorption. The limit of detection for cryogenic trapping followed by GC/ECD or GC/MS is in the low-ppt range (Krost et al. 1982; Makide et al. 1979; Rasmussen et al. 1977; Wallace et al. 1986a, 1986d). With careful technique, precision for both GC/ECD and GC/MS is acceptable, although the relative standard deviation (RSD) can be as high as ±28% (Krost et al. 1982; Rasmussen et al. 1977; Wallace et al. 1986a, 1986b, 1986c, 1986d).

Table 7-2. Analytical Methods for Determining Tetrachloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Absorbed on coconut charcoal; desorbed with carbon disulfide	GC/FID (NIOSH Method 1003)	0.4 mg/sample	96	NIOSH 1984a
Air	Air is collected in specially-prepared stainless steel canisters, concentrated on a solid sorbent and then thermally desorbed	GC/MS (EPA Method TO-15)	0.1–0.75 ppb	90–110	EPA 1999a
Air	Collected in stainless steel canister; preconcentrated in cooled adsorbent; thermally desorbed	GC/ECD	1 ppt	Not reported	Makide et al. 1979
Air	Adsorbed on Tenax-GC thermally desorbed to on-column cold trap; heat-released	HRGC/MS	1.9 ppt	Not reported	Krost et al. 1982
Air	Collected in stainless steel canister; preconcentrated by cryogenic trapping; thermally desorbed	GC/ECD	0.3 ppt	Not reported	Rasmussen et al. 1977
Air	Adsorbed on Tenax-GC; thermally desorbed to on-column cold trap; heat-released	HRGC/MS	0.3 ppt	95–99	Wallace et al. 1986a
Air	Collected in stainless steel canister (SUMMA); cryogenic preconcentration on glass beads	Full scan GC/MS (proposed EPA Method TO-14)	0.5 ppb	Not reported	Hoyt and Smith 1991
Air	Collected by passive samplers, desorbed with carbon disulfide	GC/ECD	0.1 $\mu g/m^3$	102±2	Begerow et al. 1996
Air	Air samples collected directly to a solid sorbent tube followed by thermal desorption	GC/MS (EPA Method TO-17)	0.1–0.75 ppb	90–110	EPA 1999b

Table 7-2. Analytical Methods for Determining Tetrachloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Purged and trapped in methyl silicone, 216-diphenylene oxide polymer silica gel; thermally desorbed	GC/PI (EPA 503.1)	0.01–0.05 ppb	97	APHA 1992
Water	Purged and trapped on coconut charcoal/ Tenax/silica gel; thermally desorbed	GC/MS (EPA Method 624)	1.9 ppb	101	EPA 1982b
Water	Purged and trapped on coconut charcoal/ Tenax/silica gel; thermally desorbed	GC/HSD (EPA Method 601)	0.12 ppb	106	EPA 1982b
Water	Equilibrated in sealed vial at room temperature; head-space gas injection	GC/ECD	Not reported	105	Dietz and Singley 1979
Water	Purged and trapped on Tenax-GC; thermally desorbed	GC/HECD; GC/FID	<0.1 ppb (HECD); 0.1 (FID)	98 (HECD); 79 (FID)	Otson and Williams 1982
Water	Purged and trapped on Tenax-GC; thermally desorbed	GC/HECD	Not reported	50–90	Wallace et al. 1986a, 1986d
Water	Sample directly injected	GC/UV	1 ppb	39	Motwani et al. 1986
Water	*In situ* method; concentration in LDPE coating	FEWS/FT-IR	1 ppm	Not reported	Krska et al. 1993
Water	Spray extraction; trapped in sorption tube; thermally desorbed	GC/MS	10–30 ng/L	Not reported	Baykut and Voigt 1992
Landfill leachate	Extract with pentane; analyze	GC/MS	Not reported	Not reported	Schultz and Kjeldsen 1986
Liquid and solid waste	Equilibrated in sealed via headspace gas injected	GC/HSD (EPA Method 8010)	0.03 ppb	106	EPA 1982c
Building materials and consumer products[a]	Collected by adsorption onto sorbent; thermally desorbed	HRGC/MS	0.3 ppt	Not reported	Wallace et al. 1987

Table 7-2. Analytical Methods for Determining Tetrachloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Collected in headspace vials, spiked with EPA-certified standard solvents, analysis by SPME	GC/MS	2 ng/g	Not reported	James and Stack 1996
Sediment	Spiked samples transferred to headspace analyzer	GC/MS (SIM mode)	0.2 ng/g	50.4–53.5	Kawata et al. 1997
Food	Undigested or H_2SO_4-digested samples at 90°C subjected to static head-space analysis	HRGC/ ECD; GC/MS	0.23 ppb	90–100	Entz and Hollifield 1982
Food	Extraction with isooctane; clean-up on Florisil column if needed	GC/ECD; GC/HECD	6 ppb (ECD); 13 ppb (HECD)	>50	Daft 1988
Olive oil	Add Dekalin to vial with olive oil; seal vial; incubate at 70°C for 60 minutes; inject sample of head-space gas	GC/ECD	0.02 mg/kg	Not reported	Pocklington 1992
Grains, grain-based foods	Purged and trapped on Tenax/XAD-4 resin; desorb with hexane	GC/ECD	Low- to sub-ppb	86–100	Heikes and Hopper 1986

[a]Sample is air from an environmental chamber containing the building material or consumer product.

ECD = electron capture detector; EPA = Environmental Protection Agency; FEWS = fiber evanescent wave spectroscopy; FID = flame ionization detection; FT-IR = Fourier transform infrared; GC = gas chromatography; HECD = Hall electrolytic conductivity detector; HRGC = high resolution gas chromatography; HSD = halide-sensitive detector; H_2SO_4 = sulfuric acid; LDPE = low-density polyethylene; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health; PI = photoionization; SIM = selected ion monitoring; SPME = solid-phase microextraction; UV = ultraviolet detection

The detection of tetrachloroethylene in air also was done also with dual column capillary GC with tandem ECD/FID. Detection limits were 0.01 μg/m^3 and retention times were from 18.56 to 19.24 minutes. Recovery of tetrachloroethylene was 102% (±2 standard deviation) (Begerow et al. 1996).

An alternate method of analysis chemically desorbs tetrachloroethylene from activated coconut charcoal and directly injects the extract into a GC equipped with FID detection (NIOSH 1994b; Peers 1985). The sensitivity of this method is only in the low-ppm range.

Tetrachloroethylene can be detected in drinking water, groundwater, waste water, and leachate from solid waste. The primary analytical methods are separation by GC combined with detection by HECD or other type of halogen-specific detector, ECD, or MS. In most methods, tetrachloroethylene is liberated from the liquid matrix by purging with an inert gas concentrated by trapping on a suitable solid sorbent and thermally desorbed onto the gas chromatograph column. Baykut and Voigt (1992) describe a method in which tetrachloroethylene is removed from aqueous solutions using a spray extraction technique, followed by trapping on a solid sorbent, then thermal desorption onto a gas chromatograph. Detection of tetrachloroethylene is generally by HECD (or other halogen-specific detector) or MS (APHA 1992; Baykut and Voigt 1992; EPA 1982b, 1982c; Otson and Williams 1982; Wallace 1986; Wallace et al. 1986c, 1986d). The limit of detection is in the sub-ppb range for halogen-specific detectors (APHA 1992; EPA 1982b, 1982c) and in the low-ppb for MS (EPA 1982b). Accuracy is generally >90% (APHA 1992; EPA 1982b, 1982c), although lower values have been reported (Wallace 1986; Wallace et al. 1986c, 1986d). Precision is ±13% (RSD) or better (APHA 1992; EPA 1982b, 1982c; Wallace 1986, Wallace et al. 1986d). Purging directly to the gas chromatograph with whole-column cryogenic trapping has been reported (Pankow and Rosen 1988). The study authors reported excellent purging efficiency (100%) and stated that sensitivity and precision should be correspondingly good, although specific values for these parameters were not reported. Headspace analysis has been used to determine tetrachloroethylene in water samples. High accuracy and precision were reported for a procedure in which GC/ECD was the analytical method (Dietz and Singely 1979). Solid waste leachates from sanitary landfills have been analyzed for tetrachloroethylene and other volatile organic carbons (Schultz and Kjeldsen 1986). Detection limits for the procedure, which involves extraction with pentane followed by GC/MS analysis, are in the low-ppb and low-ppm ranges for concentrated and neat samples, respectively. In addition to the GC/MS analysis, liquid chromatography (LC)/MS can be useful in detecting polar, unstable, and heavy pollutants. However, this analysis is not widely used and as such, there are not many LC/MS spectra in the literature to make comparisons to (Benfenati et al. 1996).

An *in situ* method for tetrachloroethylene analysis using fiber evanescent wave spectroscopy (FEWS) has been described by Krska et al. (1993). In this method, the water flows through a glass chamber containing a silver halide fiber coated with low-density polyethylene in an amorphous phase. The coating serves to concentrate the tetrachloroethylene, and the compound is detected using infrared spectrophotometry. The detection limit of this method, which was validated using headspace GC, was 1 ppm.

Purge-trap GC coupled with atomic emission detection is also an effective way to determine tetrachloroethylene in the water.

SPME with GC/MS was used for the determination of tetrachloroethylene in soil landfill site samples. The detection limit was 2 ng/g with the retention time of 11.0 minutes (James and Stack 1996). In sediments, headspace analysis with GC/MS was utilized for the determination of tetrachloroethylene. Recoveries ranged from 50.4 to 53.5%. Sensitivity is enhanced even further by increasing concentrations of tetrachloroethylene in the headspace gas (Kawata et al. 1997).

Several procedures for determination of the chemical in plants and food were located. GC/ECD and GC/HSD are most commonly used to analyze solid samples for tetrachloroethylene contamination. Extraction, purge-and-trap, and headspace analysis have all been used to prepare samples. Analysis of headspace gases by GC coupled with ECD, MS, or HSD has proven relatively sensitive (low- to sub-ppb range) and reproducible for a variety of foods (Entz and Hollifield 1982; EPA 1982c; Pocklington 1992). It has also been used to analyze building materials and consumer products (Wallace et al. 1987). GC/HSD of headspace gases is the EPA-recommended method for solid matrices (EPA 1982c). Foods have also been analyzed for tetrachloroethylene by GC/ECD/HECD following isooctane extraction. Sensitivity was comparable to headspace methods, but reproducibility was not as good (Daft 1988). In both headspace and extraction preparation methods, increased lipid content of the matrix adversely affected accuracy and precision. A purge-and-trap technique proved useful for analyzing grains and grain-based foods with high sensitivity and good recovery (Heikes and Hopper 1986).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tetrachloroethylene is available. Where adequate

information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tetrachloroethylene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods are available for measuring tetrachloroethylene in breath (Wallace et al. 1986a, 1986d), blood (Antoine et al. 1986; Michael et al. 1980; Ramsey and Flanagan 1982), urine (Michael et al. 1980), and adipose tissue (Chen et al. 1993; Michael et al. 1980; Ramsey and Flanagan 1982), and trichloroacetic acid in blood (Ziglio et al. 1984) and urine (Christensen et al. 1988; Pekari and Aitio 1985a, 1985b). Available methods are sensitive for measuring exposure levels at which health effects have been observed to occur (e.g., in workers known to be exposed to high levels of tetrachloroethylene). These methods have also been used to measure background levels in individuals believed not to have been exposed to higher-than-expected levels of tetrachloroethylene (e.g., office workers and housewives) (Wallace 1986). The methods are generally reliable, although increased precision for most methods would increase reliability. However, tetrachloroethylene is pervasive in the environment and background levels for the general population are not well defined. Levels may vary considerably within the environment, making it difficult to differentiate between normal background exposure and excess exposure. Further research on the relationship between levels found in living and working environments not suspected of having elevated levels of tetrachloroethylene and levels of the chemical and/or its metabolites in biological media would help in better defining background levels of the chemical and aid in determining if improved methods of monitoring exposure are needed.

Effect. There are no unique biomarkers of effect for tetrachloroethylene; however, sensitive and reliable clinical methods exist for determining damage to the liver, a target organ for tetrachloroethylene toxicity. These include measuring serum levels of liver enzymes, bilirubin, and alkaline phosphatase and urinary

urobilinogen (Bagnell and Ellenberger 1977; Coler and Rossmiller 1983; Meckler and Phelps 1966; Stewart et al. 1981). Neurological effects may also result from exposure to tetrachloroethylene (Carpenter 1937; Haerer and Udelman 1964; Hake and Stewart 1977; Kendrick 1929; Koppel et al. 1985; Morgan 1969; Rowe et al. 1952; Saland 1967; Sandground 1941; Stewart et al. 1970, 1981; Wright et al. 1937). Tests for these effects are not especially sensitive, reliable, or specific and would not improve detection over the established procedures for measuring tetrachloroethylene in breath, blood, or urine.

Methods for measuring levels of tetrachloroethylene and its metabolites that might be associated with adverse health effects are the same as those for exposure. The methods are sensitive for measuring levels of tetrachloroethylene and its metabolites in individuals not exhibiting apparent health effects resulting from the chemical (Monster and Smolders 1984; Wallace 1986) as well as in those known to be affected by absorption of excessively high levels of tetrachloroethylene. However, correlations between levels of tetrachloroethylene or its metabolites detected in biological media and specific observed effects at lower levels of absorption are not well established. Additional research in this area would allow better assessment of existing methods and would help in defining areas in which improvements are needed. Improved methods of tissue analysis, giving greater sensitivity and reproducibility, would also help in determining the quantitative relationship between the observed toxic effect on specific organs and the levels of tetrachloroethylene or its metabolites in these organs.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Existing methods for determining tetrachloroethylene in air (Krost et al. 1982; Makide et al. 1979; Rasmussen et al. 1977; Wallace et al. 1986a) and water (APHA 1992; EPA 1982b; Otson and Williams 1982), the media of most concern for human exposure, are sensitive, reproducible, and reliable for measuring background levels in the environment. Research investigating the relationship between levels measured in air and water and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed. Methods for solid matrices vary in accuracy and precision depending on the method and the matrix (e.g., sludge, soil, sediment, building material). Improved methods of detecting tetrachloroethylene in plants and foods, especially those with higher fat content, would aid in determining the contribution of tetrachloroethylene exposure from these sources. This would be especially important in determining the potential for contamination of populations living adjacent to hazardous waste sites and other potential sources of exposure to higher than background levels of tetrachloroethylene.

7.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of tetrachloroethylene and other volatile organic compounds in blood. These methods use purge and trap methodology, high-resolution gas chromatography, and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived a chronic-duration inhalation MRL of 0.006 ppm based on color vision impairment in humans chronically exposed to tetrachloroethylene in the workplace at a LOAEL of 7.3 ppm (Cavalleri et al. 1994). The LOAEL was converted to an equivalent continuous exposure concentration of 1.7 ppm (7.3 ppm × 8/24 hours × 5/7 days) and adjusted using an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL) and a modifying factor of 3 for database deficiencies (for inadequate information on potential low-dose immune system effects). The chronic-duration inhalation MRL was adopted as the acute- and intermediate-duration inhalation MRLs. A chronic-duration oral MRL of 0.008 mg/kg/day was derived based on route-to-route extrapolation from the chronic-duration inhalation MRL. The chronic-duration oral MRL was adopted as the acute- and intermediate-duration oral MRLs.

IARC has classified tetrachloroethylene as a Group 2A carcinogen (*probably carcinogenic to humans*) (IARC 2013). The World Health Organization (WHO) has established an air quality guideline value of 0.25 mg/m^3 for tetrachloroethylene as an annual average (WHO 2010) and a drinking water quality guideline value of 0.04 mg/L for tetrachloroethylene (WHO 2011).

OSHA established a permissible exposure limit (PEL) of 100 ppm for tetrachloroethylene (OSHA 2013b). OSHA has required employers of workers who are occupationally exposed to tetrachloroethylene to institute engineering controls and work practices to reduce and maintain employee exposure at or below the PEL. NIOSH has classified tetrachloroethylene as a *potential occupational carcinogen* (NIOSH 2013) and established an immediately dangerous to life or health (IDLH) value of 150 ppm. The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a threshold limit value (TLV) of 25 ppm for an 8-hour workday and a short-term exposure level (STEL) of 100 ppm (ACGIH 2012).

The American Industrial Hygiene Association (AIHA) and the Department of Energy (DOE) have established values for airborne tetrachloroethylene when responding to potential releases for use in community emergency planning (AIHA 2011; DOE 2012). These values represent increasing severity of

effects (mild, irreversible, and life threatening) for a 1-hour exposure. Tetrachloroethylene is also designated as a HAP (EPA 2013b).

EPA has classified tetrachloroethylene as *likely to be carcinogenic in humans by all routes of exposure* (EPA 2012a). NTP has classified tetrachloroethylene as *reasonably anticipated to be a human carcinogen* (NTP 2011) and ACGIH (2012) has classified tetrachloroethylene as an A3 carcinogen (*confirmed animal carcinogen with unknown relevance to humans*).

EPA (IRIS 2012) has derived an oral reference dose (RfD) for tetrachloroethylene of 0.006 mg/kg/day based on route-to-route extrapolation from the inhalation reference concentration. The EPA (IRIS 2012) inhalation reference concentration (RfC) of 0.04 mg/m^3 (0.006 ppm) for tetrachloroethylene was derived based on the midpoint between two LOAELs: 15 mg/m^3 (2 ppm) and 56 mg/m^3 (8 ppm) for two controlled human inhalation exposure studies in which neurotoxicity was observed (Cavalleri et al. 1994; Echeverria et al. 1994); an uncertainty factor of 1,000 was applied in the derivation.

EPA has designated tetrachloroethylene as a HAP under the Clean Air Act (CAA) (EPA 2013b). Tetrachloroethylene is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 100 pounds (EPA 2012f). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

Under the Toxic Substances Control Act (TSCA), tetrachloroethylene is on the list of chemicals that manufacturers and importers must report for each plant site at which they manufactured or imported tetrachloroethylene during the reporting period specified (EPA 2012j).

The international and national regulations, advisories, and guidelines regarding tetrachloroethylene in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Tetrachloroethylene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	2A[a]	IARC 2013
WHO	Air quality guidelines (annual average)	0.25 mg/m^3	WHO 2010
	Drinking water quality guidelines	0.04 mg/L	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	25 ppm	ACGIH 2012
	STEL	100 ppm	
AIHA	ERPG-1[b,c]	100 ppm	AIHA 2011
	ERPG-2	200 ppm	
	ERPG-3	1,000 ppm	
DOE	PAC-1[d]	35 ppm	DOE 2012
	PAC-2	230 ppm	
	PAC-3	1,200 ppm	
EPA	AEGL-1[e]		EPA 2013a
	10-minutes	35 ppm	
	30-minutes	35 ppm	
	60-minutes	35 ppm	
	4-hours	35 ppm	
	8-hours	35 ppm	
	AEGL-2		
	10-minutes	230 ppm	
	30-minutes	230 ppm	
	60-minutes	230 ppm	
	4-hours	120 ppm	
	8-hours	81 ppm	
	AEGL-3		
	10-minutes	1,600 ppm	
	30-minutes	1,600 ppm	
	60-minutes	1,200 ppm	
	4-hours	580 ppm	
	8-hours	410 ppm	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Tetrachloroethylene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Hazardous air pollutant	Yes	EPA 2013b 42 USC 7412
	NAAQS	No data	EPA 2013c
NIOSH	REL (10-hour TWA)	Potential occupational carcinogen	NIOSH 2013
	IDLH	150 ppm	
OSHA	PEL (8-hour TWA) for general industry	100 ppm	OSHA 2013b 29 CFR 1910.1000, Table Z-2
	Acceptable ceiling concentration	200 ppm	
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift	300 ppm for 5 minutes in any 3 hours	
	Highly hazardous chemicals	No data	OSHA 2013a 29 CFR 1910.119, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2012b 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories		EPA 2012c
	One-day (mg/L) in a 10-kg child	2 mg/L	
	Ten-day (mg/L) in a 10-kg child	2 mg/L	
	DWEL	0.5 mg/L	
	Life-time	0.01 mg/L	
	National primary drinking water standards		EPA 2009b
	MCL[f]	0.005 mg/L	
	Public health goal	Zero	
	National recommended water quality criteria: human health for the consumption of (at 10^{-4} risk)		EPA 2009c
	Water + organism	0.69 µg/L	
	Organism only	3.3 µg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2012e 40 CFR 117.3
c. Food			
FDA	EAFUS[g]	No	FDA 2013

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Tetrachloroethylene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
d. Other			
ACGIH	Carcinogenicity classification	A3[h]	ACGIH 2012
EPA	Carcinogenicity classification	Likely to be carcinogenic in humans by all routes of exposure	IRIS 2012
	RfC	0.04 mg/m^3	
	RfD	0.006 mg/kg/day	
	Oral slope factor	$2.1x10^{-3}$ per mg/kg/day	
	Inhalation unit risk	$1.8x10^{-3}$ per ppm	
	Identification and listing of hazardous waste	U210	EPA 2012d 40 CFR 261, Appendix VIII
	Inert pesticide ingredients in pesticide products approved for nonfood use only	No data	EPA 2013d
	Master Testing List	Yes[i]	EPA 2013e
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	Yes	EPA 2012f 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity pursuant to Section 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA	100 pounds	EPA 2012g 40 CFR 302.4
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2012h 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2012i 40 CFR 355, Appendix A
	TSCA chemical lists and reporting periods	No data	EPA 2012j 40 CFR 712.30
	TSCA health and safety data reporting		EPA 2012k 40 CFR 716.120
	Effective date	06/01/1987	
	Reporting date	06/01/1997	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Tetrachloroethylene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2011

[a]Group 2A: probably carcinogenic to humans.
[b]ERPG-1: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odor; ERPG-2: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action; ERPG-3: is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects (AIHA 2011).
[c]Odor should be detectable near ERPG-1.
[d]PAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects (DOE 2012).
[e]AEGL-1: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects; however, these effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape; AEGL-3: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death (EPA 2013a).
[f]Potential health effects from long-term exposure above the MCL could cause liver problems and increased risk of cancer; common sources of contaminant in drinking water include discharges from factories and dry cleaners (EPA 2009b).
[g]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[h]A3: confirmed animal carcinogen with unknown relevance to humans.
[i]Testing action development underway for acute development and immunological health effects.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminat level; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure level; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: February 2014
Profile Status: Draft for Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 128
Species: Human

Minimal Risk Level: 0.006 [ ] mg/kg/day [x] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Experimental design: See worksheet for chronic inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic inhalation MRL.

Dose and end point used for MRL derivation: See worksheet for chronic inhalation MRL.

[ ] NOAEL [x] LOAEL

1.7 ppm

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: Data available for acute-duration inhalation MRL derivation include three controlled human exposure studies and several animal studies. The lowest effect levels were identified in the human exposure studies by Altmann et al. (1990, 1992). In the study by Altmann et al. (1992), male volunteers were exposed to tetrachloroethylene at 10 or 50 ppm, 4 hours/day for 4 days. Corresponding equivalent continuous exposure concentrations are 2 and 10 ppm. At 50 ppm, pattern reversal visual-evoked potential latencies increased ($p<0.05$) and significant performance deficits for vigilance ($p=0.04$) and eye-hand coordination ($p=0.05$) were

observed. No effects on brainstem auditory-evoked potential were noted at either concentration. Because a faint odor was reported by 33% of the subjects at 10 ppm and 29% of the subjects at 50 ppm on the first day of testing, and by 15% of the subjects at 10 ppm and 36% of the subjects at 50 ppm on the last day of testing, the investigators concluded that only a few subjects could identify their exposure condition. In a similar study by Altmann et al. (1990), significant ($p<0.05$) increased latencies for pattern reversal visual-evoked potentials were observed in 10 male volunteers exposed to tetrachloroethylene at 50 ppm, compared to 12 men exposed at 10 ppm. Exposures in this study were also 4 hours/day for 4 days, resulting in equivalent continuous exposure concentrations of 2 and 10 ppm. Effects on brainstem auditory-evoked potentials were not observed in the Altmann et al. (1990) study. Tetrachloroethylene in the blood increased with exposure duration, and linear regression to associate blood tetrachloroethylene with pattern reversal visual-evoked potential latencies was significant ($r=-0.45$, $p<0.03$). Additional tests of neurological function were not conducted in this study. These two studies identified a NOAEL of 10 ppm (2 ppm equivalent continuous exposure concentration).

Hake and Stewart (1977) did not find any changes in flash-evoked potentials or equilibrium tests in four male subjects exposed to increasing concentrations of tetrachloroethylene 7.5 hours/day for 5 days. The subjects were sequentially exposed to 0, 20, 100, and 150 ppm (each concentration 1 week). Corresponding equivalent continuous exposure concentrations are 6.25, 31, and 47 ppm. Subjective evaluation of EEG scores suggested cortical depression in subjects exposed at 100 ppm. Decreases in the Flanagan coordination test were observed at ≥100 ppm.

Animal studies of acute-duration exposure to tetrachloroethylene have demonstrated neurological effects, but at higher concentrations than the human study by Altmann et al. (1990) (>16 ppm continuous equivalent concentration; Boyes et al. 2009; DeCeurriz et al. 1983; Mattsson et al. 1998; NTP 1986; Oshiro et al. 2008; Savolainen et al. 1977). PBPK modeling simulations suggest equivalent tetrachloroethylene blood AUCs for rats and humans exposed to the same inhaled concentrations (Chiu and Ginsberg 2011), indicating that the human-equivalent concentrations for these studies are also ≥16 ppm and higher than the human effect levels identified by Altmann et al. (1990, 1992). Thus, animal studies were not considered to be suitable options for acute-duration MRL derivation.

An acute-duration inhalation MRL could be obtained using the controlled human exposure study by Altmann et al. (1990, 1992). This study identified a NOAEL of 2 ppm (equivalent continuous exposure concentration) for neurobehavioral changes. This value is equal to the LOAEL of 1.7 ppm for color vision decrements in the chronic-duration epidemiological study by Cavalleri et al. (1994). Given that the NOAEL was from a study in which exposures were for only 4 hours per day for 4 days, it is uncertain whether this value would be adequately protective for longer exposures (up to 2 weeks). In male volunteers exposed to 1 ppm tetrachloroethylene for 6 hours, venous blood concentrations continued to increase between 4 and 6 hours (Chiu et al. 2007); likewise, when venous blood was sampled before each of four daily 4-hour exposures to tetrachloroethylene at 10 or 50 ppm, concentrations continued to increase each day from 36 µg/L before the second exposure to 10 ppm up to 56 µg/L 1 day after the fourth daily exposure (Altmann et al. 1990). These data suggest that continuous or repeated exposures over durations longer than 4 days may yield higher blood levels than seen after four daily 4-hour exposures, and that the NOAEL of 2 ppm observed in the study by Altmann et al. (1990) may not be adequately protective for exposures up to 2 weeks. Because it is very close to the NOAEL from acute-duration exposure, the chronic-duration LOAEL of 1.7 ppm (continuous equivalent exposure concentration) from Cavalleri et al. (1994) may represent a better basis for acute and intermediate-duration MRLs. A PBPK model (Chiu and Ginsberg 2011) was used to evaluate the effect of exposure duration on the AUC of the blood concentration-time curve at a continuous exposure of 1.7 ppm. This simulation showed that the 24-hour AUC blood concentration-time values are very similar after 14 days, 90 days, 365 days, and 2 years of exposure (see Table A-1 below). These simulations predict that the blood AUC of tetrachloroethylene is nearly constant after 2 weeks of continuous exposure. The blood concentration

reaches approximately 90% of reaches steady-state at about 2 weeks of continuous exposure and 99% of steady state at 90 days. Given that the tetrachloroethylene AUC after acute-duration exposure is very similar to that after chronic exposure to the same concentration, the chronic MRL was adopted as the acute-duration MRL.

Table A-1. Predicted Effect of Exposure Duration on Human Blood Levels of Tetrachloroethylene During Continuous (24 Hours/day, 7 Days/week) Inhalation Exposure to 1.7 ppm

	Exposure duration (days)			
PBPK dose metric	14	90	365	728
Area under the blood concentration-time curve (mg-24 hour/L per ppm)	1.799	1.999	2.029	2.033

Agency Contact (Chemical Manager): Robert Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: February 2014
Profile Status: Draft for Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 128
Species: Human

Minimal Risk Level: 0.006 [ ] mg/kg/day [x] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Experimental design: See worksheet for chronic inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic inhalation MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

1.7 ppm

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: Available intermediate-duration studies that examined or observed neurological or neurobehavioral effects in animals (e.g., Karlsson et al. 1987; Kyrklund et al. 1988, 1990; Mattsson et al. 1992, 1998; Rosengren et al. 1986; Tinston 1995; Wang et al. 1993) identified effect levels much higher than the acute-duration human studies (Altmann et al. 1990, 1992; Hake and Stewart 1977). In addition, the available data suggest that low effect levels in humans from acute-duration exposure are similar to those for the chronic-duration LOAEL of 1.7 ppm (continuous equivalent exposure concentration) from Cavalleri et al. (1994),

suggesting that the same MRL may be applicable to all exposure durations. A PBPK model (Chiu and Ginsberg 2011) was used to evaluate the effect of exposure duration on the AUC of the blood concentration-time curve at a continuous exposure of 1.7 ppm. This simulation showed that and 24-hour AUC values are very similar after 14 days, 90 days, 365 days, and 2 years of exposure (see Table A-2). These simulations predict that the blood AUC of tetrachloroethylene is nearly constant after 2 weeks of continuous exposure. The blood concentration reaches approximately 90% of reaches steady-state at about 2 weeks of continuous exposure and 99% of steady state at 90 days. Given that the tetrachloroethylene AUC after intermediate-duration exposure is the same as that after chronic exposure to the same concentration, the chronic MRL was adopted as the intermediate-duration MRLs.

Table A-2. Predicted Effect of Exposure Duration on Human Blood Levels of Tetrachloroethylene During Continuous (24 Hours/day, 7 Days/week) Inhalation Exposure to 1.7 ppm

	Exposure duration (days)			
PBPK dose metric	14	90	365	728
AUC (mg-24 hour/L per ppm)	1.799	1.999	2.029	2.033

Agency Contact (Chemical Manager): Robert Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: February 2014
Profile Status: Draft for Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 128
Species: Human

Minimal Risk Level: 0.006 [ ] mg/kg/day [x] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196-198.

Experimental design: Color vision was evaluated in 35 tetrachloroethylene-exposed workers (22 dry cleaners and 13 ironers) with an average of 106 months of exposure. Concentrations were measured in the breathing zone by personal passive samplers. The TWA concentrations for all workers ranged from 0.38–31.19 ppm, with mean exposures of 6.23, 7.27, and 4.80 ppm for all workers, dry cleaners, and ironers, respectively. Controls included an equal number (35) of workers without occupational exposure to solvents, and were matched for sex, age, alcohol consumption, and cigarette smoking. Color vision was evaluated by the Lanthany 15 Hue desaturated panel (D-15d) test, which is designed for early detection of acquired dyschromatopsia. The results of the test were expressed as color confusion index (CCI). The subjects were reexamined 2 years later using the same test; results were reported by Gobba et al. (1998).

Effects noted in study and corresponding doses: The results of the color vision test showed a significant decrease in color vision (mainly blue-yellow range) in the dry cleaners exposed to a mean concentration of 7.3 ppm. The results of multivariate analysis demonstrated lack of correlation with age, alcohol, etc. Mean (±standard deviation) CCI scores were 1.192±0.133 in dry cleaners compared with 1.089±0.117 in controls ($p=0.007$). Reexamination of the workers 2 years later showed that those workers whose exposure to tetrachloroethylene had increased (from a geometric mean concentration of 1.67 to 4.35 ppm, $p<0.01$) experienced further decrements in color vision (from a mean CCI of 1.16 to 1.26, $p<0.01$), while those whose exposure had decreased (from a geometric mean concentration of 2.95 to 0.66 ppm) experienced no change in CCI (Gobba et al. 1998). The 7.3 ppm concentration was multiplied by 8/24 hours and 5/7 days to yield an equivalent continuous exposure concentration of 1.7 ppm. The 1.7 ppm concentration was considered a LOAEL for decreased color vision and was used to derive the chronic MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

1.7 ppm, increased CCI

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose; was a conversion used from intermittent to continuous exposure? To convert from occupational exposure to continuous exposure, the 7.3 ppm concentration was multiplied by 8/24 hours and 5/7 days to yield an equivalent continuous exposure concentration of 1.7 ppm.

Other additional studies or pertinent information which lend support to this MRL: The nervous system is a well-established target of tetrachloroethylene exposure in humans and animals, and effects on this system occur at lower concentrations than effects in other target organs such as the liver or kidney. There is a substantial number of studies evaluating the effects of inhaled tetrachloroethylene in occupationally exposed individuals, particularly those engaged in dry cleaning activities. More recent studies have also examined residential populations living in buildings that also housed dry cleaning facilities or in buildings in close proximity to such facilities. The human epidemiological studies (especially Cavalleri et al. 1994; Echeverria et al. 1995; Gobba et al. 1998; Schneiber et al. 2002; Storm et al. 2011), combined with a small number of human controlled exposure experiments (Altmann et al. 1990; Hake and Stewart 1977), have identified central nervous system effects after acute-, intermediate-, and chronic-duration exposures to tetrachloroethylene.

Storm et al. (2011) recruited adults and children living in New York City buildings with or without colocated dry cleaners for a larger study of visual acuity and contrast sensitivity. There were a number of differences between the exposed and referent groups with respect to education, race/ethnicity, and income. The exposed subjects were stratified into low and high exposure (<100 or >100 $\mu g/m^3$ tetrachloroethylene) based on 24-hour air samples; exhaled air and blood were also analyzed for tetrachloroethylene. Geometric mean indoor air concentrations of 0.00046, 0.0018, or 0.050 ppm tetrachloroethylene were reported for the referent, low, and high exposure groups of children (n=56, 39, and 11, respectively); for adult participants, the respective concentrations were 0.00043, 0.0017, or 0.070 ppm (n=49, 43, and 12, respectively). Visual acuity testing was limited to far distance visual contrast only, and the response was scored as either perfect or less than perfect. In children, a higher concentration of tetrachloroethylene in indoor air was associated with a higher odds of achieving less than the maximum score (in the poorer performing eye) at a spatial frequency of 12 cycles per degree of visual arc; the effect remained after adjustment for race, ethnicity, and age (adjusted OR of 2.64; 95% CI 1.41–5.52). Visual contrast sensitivity of adults was not associated with measures of tetrachloroethylene exposure. Due to the limitations of this study, including the use of an insensitive vision test and differences between exposed and referent populations that were not accounted for, this study is not considered to be a candidate for MRL derivation.

Schreiber et al. (2002) evaluated a group of residents (n=17) and a group of daycare workers (n=9), each of whom was exposed to tetrachloroethylene for an average of 4 or 5.8 years, respectively, originating from a dry cleaner that was co-located with the residence or daycare. Age- and sex-matched controls without exposure consisted of NYSDOH employees. Visual acuity, color discrimination, and contrast

sensitivity were assessed in these groups; investigators involved in vision testing were not blinded to the exposure status. Ambient and personal air monitoring results suggested mean concentrations of about 0.11 ppm among the residents and about 0.3 ppm among the daycare workers. In both groups, significant ($p<0.001$) decreases in visual contrast sensitivity were observed when compared with the unexposed referent groups. Due to limitations of this study including: small sample size (17 exposed and 17 controls), selection bias in choice of referent population (NYSDOH employees), and vision testing by investigators not blinded to exposure status, it was not selected for use in MRL derivation.

Altmann et al. (1995) evaluated neurobehavioral effects of tetrachloroethylene in 14 persons living above or next to dry cleaning facilities for 1–30 years compared with 23 unexposed controls. The median concentrations of tetrachloroethylene were 0.2 and 0.003 ppm in the apartments of exposed and control subjects, respectively; blood concentrations measured in the examination room (not in the apartments) were 17.8±46.9 µg/L (mean±standard deviation) in exposed subjects and below the 0.5 µg/L detection limit in controls. A neurological test battery, including pattern reversal visual-evoked potentials, continuous performance test, hand-eye coordination, finger tapping, simple reaction time, and visual memory, was administered to both groups. No significant differences between the groups were observed when the unadjusted test results were compared (Altmann et al. 1995). However, when results were analyzed using multivariate analysis to adjust for age, gender, and education, response time in the continuous performance test and simple reaction time were increased ($p<0.05$), and a smaller number of stimuli were identified correctly by the exposed subjects ($p<0.05$) relative to 23 controls. Limitations of this study include its small sample size and differences in educational level between the exposed and referent groups.

Performance on neurobehavioral tests was also assessed in a study of 65 dry cleaning workers exposed to tetrachloroethylene for at least 1 year (Echeverria et al. 1995). The workers were grouped into low, medium, or high exposure categories based on job title and years of employment. Exposure estimates for the three categories were based on air concentrations measured in the breathing zone of clerks, pressors, and operators (8-hour TWA concentrations were 11.2, 23.2, and 40.8 ppm, respectively). Neurobehavioral tests that measured short-term memory for visual designs showed deficits in the high-exposure group (40.8 ppm) relative to the low-exposure group (11.2 ppm). After adjustment for potential confounding, scores for pattern recognition, pattern memory, and visual reproduction were significantly reduced (4, 7, and 14%, respectively; $p<0.01$) in the high-exposure group compared with the low-exposure group. Echeverria et al. (1995) also described four cases referred for neuropsychologic assessment of possible tetrachloroethylene encephalopathy. The subjects performed below expectation on tasks assessing memory, motor, visuospatial, and executive functions, with milder attentional deficits.

Neurological effects of tetrachloroethylene exposure in laboratory rodents are qualitatively similar to those seen in human studies. Mice and rats have exhibited anesthetic effects after acute exposure to high concentrations of tetrachloroethylene (Friberg et al. 1953; Goldberg et al. 1964; NTP 1986; Rowe et al. 1952). Rats exposed to 3,000 ppm tetrachloroethylene became anesthetized in several hours, while those exposed to 6,000 ppm were anesthetized in minutes (Rowe et al. 1952). Anesthesia was observed in mice within 2.5 minutes of breathing air containing 6,800 ppm tetrachloroethylene (Friberg et al. 1953). Mice inhaling tetrachloroethylene for 4 hours showed signs of anesthesia at a concentration of 2,328 ppm (NTP 1986). Rats became ataxic following exposure to 2,300 ppm for 4 hours (Goldberg et al. 1964). Dyspnea, hypoactivity, hyperactivity, anesthesia, and ataxia were noted in mice and rats exposed to 1,750 ppm for 6 hours/day, 5 days/week for 2 weeks; these effects were not seen at lower concentrations (up to 875 ppm) (NTP 1986). Lower concentrations have resulted in effects on visual-evoked potentials (Albee et al. 1991; Boyes et al. 2009; Mattsson et al. 1998), EEG patterns (Albee et al. 1991), and neurobehavioral tests (Oshiro et al. 2008; Savolainen et al. 1977), as well as brain chemistry (Karlsson et al. 1987; Kyrklund et al. 1988; Rosengren et al. 1986; Wang et al. 1993) in laboratory rodents or gerbils. Male Long-Evans rats exposed for 1.5 hours to concentrations of 250, 500, or 1,000 ppm exhibited

reduced amplitude of visual evoked potentials at all exposure concentrations (Boyes et al. 2009). Albee et al. (1991) reported electrophysiological changes including altered shape, reduced amplitude, and decreased latency of flash-evoked potentials; decreased latency of somatosensory evoked potentials; and EEG changes in male rats exposed to tetrachloroethylene at 800 ppm 4 hours/day for 4 days. Similar findings were observed when male F344 rats were exposed 6 hours/day for 4 days to 800 ppm tetrachloroethylene as a pilot study in preparation for a subchronic study (Mattsson et al. 1998). Impairment of sustained attention was observed in male Long-Evans rats exposed for 1 hour to concentrations ≥500 ppm tetrachloroethylene (Oshiro et al. 2008). Open-field behavior (ambulation) was elevated in groups of 10 male rats exposed to 200 ppm tetrachloroethylene of unspecified purity for 6 hours/day for 4 days (Savolainen et al. 1977). Ambulation was significantly increased 1 hour, but not 17 hours, after the last exposure (Savolainen et al. 1977).

In addition, brain chemistry has been altered in laboratory rodents or gerbils exposed to tetrachloroethylene (Karlsson et al. 1987; Kyrklund et al. 1984, 1988; Rosengren et al. 1986; Wang et al. 1993). Gerbils exposed to 320 ppm continuously for 3 months followed by a 4-month exposure-free period had changes in levels of S-100 protein, a marker for astrocytes as well as other cells in the peripheral nervous system and skin (Rosengren et al. 1986). Rats exposed to 320 ppm continuously for 30 days had changes in brain cholesterol, lipids, and polyunsaturated fatty acids (Kyrklund et al. 1988). Changes in the fatty acid composition of the brain were also observed in rats continuously exposed to tetrachloroethylene at 320 ppm for 90 days (Kyrklund et al. 1990). Gerbils exposed to 60 or 320 ppm had decreased DNA content in portions of the cerebrum (Karlsson et al. 1987; Rosengren et al. 1986). Gerbils exposed to 120 ppm continuously for 12 months had altered phospholipid content (phosphatidylethanol-amine) in the cerebral cortex and hippocampus (Kyrklund et al. 1984). In rats exposed to 600 ppm tetrachloroethylene continuously for 4 weeks, cytoskeletal elements of neuronal cells (neurofilament 68 kD polypeptide) were significantly reduced in the frontal cerebral cortex, hippocampus, and brainstem; after 12 weeks at this concentration, a cytosolic marker (glial S-100) and cytoskeletal elements of glial cells (glial fibrillary acid protein) were also significantly reduced in all three brain regions (Wang et al. 1993).

Agency Contact (Chemical Manager): Robert Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: February 2014
Profile Status: Draft for Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 128 (see Figure 3-1)
Species: Human

Minimal Risk Level: 0.008 [x] mg/kg/day [ ] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196-198.

Experimental design: See worksheet for chronic-duration inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic-duration inhalation MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

2.3 mg/kg/day, increased CCI, estimated by route-to-route extrapolation from continuous-equivalent inhalation exposure concentration of 1.7 ppm.

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic-duration inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: There is abundant evidence for neurological and neurobehavioral effects after chronic, low exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure

are expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg [2011]). Among human and animal studies identifying neurological or neurobehavioral effects after acute-duration oral exposure, the lowest effect level was identified by Fredrikkson et al. (1993). Fredriksson et al. (1993) identified a LOAEL of 5 mg/kg/day for hyperactivity in male NMRI mice exposed via gavage for 7 days beginning on postnatal day 10 (Fredriksson et al. 1993). Significant pharmacokinetic differences between mice and humans lead to markedly different blood levels of parent compound after oral exposure to tetrachloroethylene; thus, mice are not a good model for neurological effects of tetrachloroethylene exposure in humans. Other acute-duration studies evaluating neurological responses used doses at least 10-fold higher. In addition, the LOAEL of 5 mg/kg/day identified in mice is similar to the POD of 2.3 mg/kg/day for the chronic oral MRL. Given the lack of suitable acute-duration oral data, and the observation that neurobehavioral effect levels for acute-duration exposure in humans are similar to those for chronic-duration exposure, the acute oral MRL was set equal to the chronic oral MRL.

Agency Contact (Chemical Manager): Robert Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: February 2014
Profile Status: Draft for Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 128 (see Figure 3-1)
Species: Human

Minimal Risk Level: 0.008 [x] mg/kg/day [ ] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196-198.

Experimental design: See worksheet for chronic-duration inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic-duration inhalation MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

2.3 mg/kg/day, increased CCI, estimated by route-to-route extrapolation from continuous- equivalent inhalation exposure concentration of 1.7 ppm.

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic-duration inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: There is abundant evidence for neurological and neurobehavioral effects at low exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure are

expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg [2011]). Among human and animal studies of intermediate-duration oral exposure, only Chen et al. (2002) examined sensitive neurological or neurobehavioral effects. An intermediate-duration 8-week study by Chen et al. (2002) identified a LOAEL of 5 mg/kg/day (adjusted to equivalent continuous dose of 3.6 mg/kg/day based on administration on 5 days/week) for impaired nociception (increased latency to tail withdrawal from hot water and increased response latency to hot plate tests) and increased threshold for pentylenetetrazol-induced seizure initiation. PBPK modeling results reported by Chiu and Ginsberg (2011) indicate that the area under the tetrachloroethylene blood concentration-time curve for humans is about twice that of rats across a wide range continuous oral doses (0.01–1,000 mg/kg/day). Thus, the human-equivalent LOAEL dose from the study by Chen et al. (2002) is 1.8 mg/kg/day. This LOAEL is virtually identical to the human oral LOAEL of 2.3 mg/kg/day obtained by route-to-route extrapolation from the Cavalleri et al. (1994) chronic inhalation study. Because the human data provide a better basis for MRL derivation than the rat data, the chronic-duration oral MRL was applied to all exposure durations.

It should be noted that the lowest effect levels for acute- or intermediate-duration oral exposure to tetrachloroethylene were from rat and mouse studies of drinking water exposures examining immune stimulation. Seo et al. (2008a, 2012) observed enhancement of antigen-stimulated allergic responses in rats and mice exposed to estimated doses of 0, 0.0009, or 0.09 mg/kg/day (rats) and 0, 0.0025, or 0.26 mg/kg/day (mice) tetrachloroethylene administered in drinking water for 2 or 4 weeks. Little support for the observed enhancement of allergic response has been shown in other animal studies of tetrachloroethylene exposure, and few human data pertaining to immune system effects of tetrachloroethylene are available. The studies by Seo et al. (2008a, 2012) were considered for MRL derivation. However, the evidence for enhanced allergic responses after oral tetrachloroethylene exposure is limited to studies from a single laboratory using small numbers of animals (4–6 per group) and uncertain dose estimates, and support for immune system perturbation in animals or humans exposed to tetrachloroethylene is lacking. Furthermore, the effects reported by Seo and coworkers (enhanced passive and active cutaneous anaphylaxis, increased histamine release, etc.) are of uncertain toxicological and human health relevance, as it is unclear when these responses can be considered adverse. Due to the lack of supporting evidence for immune system perturbation, unclear relevance of the enhanced allergic response to humans, and uncertainty regarding when such an effect is considered adverse, these studies were not used for oral MRL derivation.

Agency Contact (Chemical Manager): Robert Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: February 2014
Profile Status: Draft for Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 128 (see Figure 3-1)
Species: Human

Minimal Risk Level: 0.008 [x] mg/kg/day [ ] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196-198.

Experimental design: See worksheet for chronic-duration inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic-duration inhalation MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

2.3 mg/kg/day, increased CCI, estimated by route-to-route extrapolation from continuous- equivalent inhalation exposure concentration of 1.7 ppm. The internal dose metric chosen for route-to-route extrapolation was the 24-hour AUC of the tetrachloroethylene blood concentration-time curve. While it is not certain whether the neurological effects of tetrachloroethylene result from the parent compound or one or more of its metabolites, the AUC of the tetrachloroethylene blood concentration-time curve is assumed to represent a reasonable surrogate for the internal dose of the ultimate toxicant(s). In addition, Chiu and Ginsberg (2011) showed that alternative dose metrics (based on metabolites) yielded minimal differences in route-to-route extrapolation (within 1.4-fold of the extrapolation based on blood AUC). Based on simulations of the Chiu and Ginsberg (2011) model, a continuous inhalation exposure to 1.7 ppm yields the same 24-hour AUC as a continuous oral dose of 2.3 mg/kg/day.

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic-duration inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: The available human epidemiological studies of oral exposure to tetrachloroethylene do not provide sufficient exposure information to identify effect levels, and are thus not suitable for oral MRL derivation. The only available chronic-duration oral study of tetrachloroethylene in animals is the NCI (1977) cancer bioassay. In this study, survival was decreased at the lowest dose in both rats and mice; thus, it is also not suitable for use in deriving a chronic-duration oral MRL.

There is abundant evidence for neurological and neurobehavioral effects after chronic, low exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure are expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg [2011]). Given the lack of suitable chronic-duration oral data, and the availability of a robust PBPK model for route-to-route extrapolation, the chronic-duration MRL was derived by route-to-route extrapolation from the chronic-duration inhalation MRL using the PBPK model.

Agency Contact (Chemical Manager): Robert Williams

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgment, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

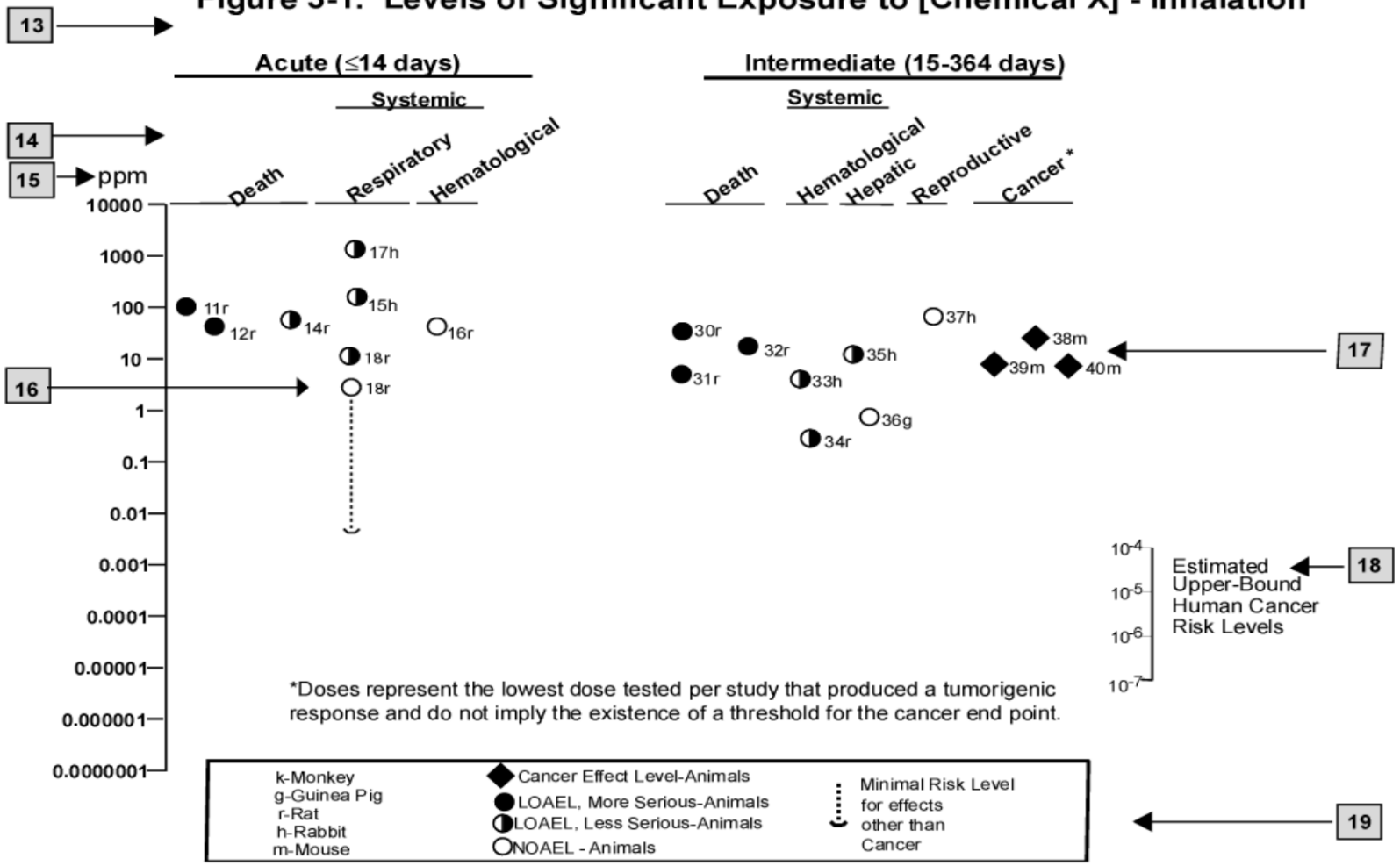
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX